UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF PENNSYLVANIA

IN RE: TYLENOL (ACETAMINOPHEN) MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	§	**MDL NO. 2436** **2:13-md-02436** **HON. LAWRENCE F. STENGEL**
This Document Relates to: Rana Terry, as Personal Representative and Administrator of the Estate of Denice Hayes, Deceased, Plaintiff, vs. McNEIL-PPC, Inc., McNeil Consumer Healthcare, and Johnson & Johnson, Inc., Defendants.	§	Civil Action No. 2:12-cv-07263

M E M O R A N D U M

Stengel, J. **July 14, 2016**

A key issue to be decided in this multi-district litigation is whether acetaminophen in Tylenol products can cause acute liver failure (ALF) at or just above the recommended dose. To establish the causal link between acetaminophen at recommended doses and

ALF, the plaintiff plans to use the testimony and opinions of several experts.[1] In forming their opinions, plaintiff's experts rely on an article entitled "Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study" (Larson, et al., Hepatology, Vol. 42, No. 6, 2005).[2] One section of this article indicates that acetaminophen-induced ALF can occur at the maximum daily recommended dose of 4 grams.

The defendants move to exclude use of this article by plaintiff or her experts under Daubert.[3] For the reasons stated below, I will deny this motion.

I. Procedure of this Motion: Release of the Larson Article Data and Litigation in New Jersey and Texas[4]

In December 2015, the defendants requested leave from this court to supplement expert reports for pending Daubert motions.[5] They claimed they had recently received data that would undermine the findings in one of the key articles relied on by plaintiffs' causation experts. This article, entitled "Acetaminophen-Induced Acute Liver Failure:

[1] See, e.g., Neil Kaplowitz, M.D. Expert Report, May 5, 2014 at 8 (Doc. No. 154, Ex. 15); N. Kaplowitz Dep., June 3, 2014 at 45, 47, 176 (while the "vast majority of people who take therapeutic doses of Tylenol do not get into trouble," there are "individuals – rare, but [a] finite number of individuals in the world who develop serious liver injury, including acute liver failure, when at or near the therapeutic maximum dose, as it was, 4 grams a day and possibly even 3 grams a day.")(Doc. No. 154, Ex. 9); T. Davern Dep., Mar. 28, 2015 at 126, 137 ("Q. And is it your representation that that paper stands for the proposition that four grams per day in those patients caused acute liver failure? A. Yes. Again, in this study, that was our conclusion.")(Doc. No. 155, Ex. 3).

[2] See Doc. No. 193, Ex. A.

[3] Though its title suggests that the defendants are asking for the exclusion of certain plaintiff's expert opinions, in reality, the defendants want the court to exclude the use of the Larson article itself. I will address the admissibility of the plaintiff's expert opinions themselves in my decisions on their Daubert challenges, which are already pending.

[4] See Defendants' Motion for Leave to File Supplemental Reports, Dec. 8, 2015 (Doc. No. 186) and Plaintiff's Response in Opposition, Dec. 15, 2015 (Doc. No. 187) for the information contained in this section.

[5] See Doc. No. 186.

Results of a United States Multicenter, Prospective Study" (hereinafter, "The Larson article"), was published in 2005 by the Acute Liver Failure Study Group (ALFSG). See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372 (Doc. No. 193, Ex. A).

Unbeknowst to this court, the defendants had requested the data underlying the findings in the Larson article a year and half prior. [6] On March 25, 2014, Judge Carol Higbee, who was presiding over parallel New Jersey litigation, permitted the defendants to subpoena these documents to use during the deposition of William Lee, M.D. Dr. Lee is the principal investigator for the ALFSG and is a Professor of Internal Medicine at the University of Texas Southwestern Medical Center in Dallas, TX.[7] He is one of the nation's foremost authorities in drug induced liver injury (DILI) and has been involved with the FDA Advisory Committee meetings on the topic of acetaminophen-induced liver injury.[8] The plaintiff planned to call Dr. Lee as a third-party fact witness in the New Jersey litigation. He was not being retained as an expert or consultant for the plaintiff.

The defendants then instituted a separate proceeding in state court in Dallas, Texas because the ALFSG case data was maintained at the University of Texas Southwestern (UTSW).[9] Dr. Lee and UTSW, represented by the Texas Attorney General's Office,

[6] This was the first time I was informed of the proceedings happening in Texas.

[7] See William Lee, M.D. Dec., May 10, 2016 at ¶¶ 7, 10 (Doc. No. 220)(filed under seal).

[8] See, e.g., William Lee, M.D. Dec., May 10, 2016 at ¶¶ 7, 19, 26 (Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 31-35 (Doc. No. 216, Ex. 3).

[9] Proceedings were also initiated in South Carolina related to another ALFSG center, the Medical University of

opposed production of the ALFSG data.[10] On October 9, 2014, after hearing argument, the Texas presiding judge ordered UTSW to produce the requested documents. UTSW began producing the documents on a rolling basis in early November 2014. Two Rule 11 Agreements were put in to place to safeguard patients' confidential health information.

The bulk of the information was produced between October 2014 and September 2015.[11] The last production of documents occurred in late November 2015. The defendants filed their motion for leave to supplement their reports here in early December.[12] They claimed the data received from the ALFSG undermined the Larson article's finding that acetaminophen-induced ALF could be caused by recommended doses. The defendants argued that their "ability to present highly relevant data and opinions to the jury" would be "critically impaired" if they were not permitted to submit expert opinions on the "newly disclosed" data and that their due process rights would be violated.[13] They contended the new data showed the article's methodology was flawed.

South Carolina. The two centers cooperated and information was produced from UTSW.

[10] Initially, the defendants requested all of the ALFSG data from Dr. Lee. Through counsel at the Texas Attorney General's office, he opposed production of any information and asserted that he personally did not have possession of ALFSG's data. The defendants then sought the information from UTSW, which moved to quash the subpoena. The ALFSG and Dr. Lee opposed this production because of concerns about the confidentiality of patient information. See W. Lee Dep., Apr. 14, 2016 at 128-29 (Doc. No. 216, Ex. 3). The plaintiff opposed this request in New Jersey. Judge Nelson Johnson, who was assigned the New Jersey cases after Judge Higbee was elevated to the appellate bench, denied this request.

[11] The request to Judge Higbee occurred during pre-trial proceedings in Lyles v. McNeil, et al., the first of the New Jersey cases to be scheduled for trial. During the Texas litigation of this issue, the Lyles case settled. Judge Nelson Johnson took over supervision of the New Jersey Tylenol cases, after Judge Higbee was elevated to the appellate bench. Because of the timing of production, the ALFSG Larson data was not considered during Jackson v. McNeil, et al.—the first New Jersey case that was tried in September 2015 before Judge Johnson.

[12] See Doc. No. 186.

[13] Doc. No. 186 at 2.

The plaintiff opposed the motion.[14] The plaintiff argued that the motion was "little more than a late in the day side show" to delay the first bellwether trial set in this MDL. After hearing argument from the parties in January, I granted the defendants leave to supplement their expert opinions.[15] I wanted to ensure that this issue was fully explored. The defendants submitted their supplemental reports and moved to exclude the Larson article. In response, the plaintiff moved to strike the defense experts' supplemental reports, arguing that *those* reports were flawed under Daubert.

After motions practice, I scheduled argument on the ALFSG motions for April. The defendants requested that argument be postponed until July.[16] I denied this request. The parties argued these motions on April 27, 2016 at a monthly status conference.

II. The ALFSG and the "Larson article"

The Larson article was authored by several members of the ALFSG. The lead author on this article was Dr. Anne Larson.[17] Dr. Lee and plaintiff's expert Dr. Timothy

[14] See Doc. No. 187.

[15] I denied the defendants' request for the experts to be re-deposed. The defendants filed the same motion in parallel New Jersey litigation. Judge Johnson allowed the parties to re-depose experts on the ALFSG data. The defendants requested that the depositions be cross-noticed in a March 7, 2016 letter to the court; the plaintiff did not object to this request. I allowed the parties to cross-notice these depositions in this litigation, at their request.

The defendants have since supplemented the record with the transcripts of those depositions that were taken. Though I denied their request for these depositions, I did review those transcripts in making my decision.

[16] The defendants argued that not all of the expert depositions had been taken. The parties would then be unable to argue the motions in May or June because they would be preparing for trial in the parallel litigation in New Jersey. When the defendants filed this late-in-the-game motion, they had assured me that this issue would not delay trying the Terry/Hayes case. Pushing argument back to July would likely have caused delays in the trial schedule already in place. Since then, the defendants' arguments have been mooted. They have supplemented the record with depositions not available at the time of argument, which I have reviewed.

[17] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1364 (Doc. No. 193, Ex. A); Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 2 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal).

Davern are also named authors.[18] The ALFSG is the leading research group in the United States on ALF in adults. It is comprised of more than forty physicians, researchers, and medical professionals from over twenty medical centers and teaching institutions in the United States.[19] It was established in 1997 to study the relatively rare disease of ALF. To accomplish this goal, the ALFSG collects data and biosamples at its sites. For almost twenty years, the ALFSG has been funded by the U.S. Food and Drug Administration (FDA) and the National Institute of Health (NIH).[20] During that period, it has published more than sixty peer-reviewed publications. Data from the ALFSG registry has been relied on by the FDA, NIH, and other medical professionals.[21]

Close to 130,000 pages of documents were produced from the ALFSG. The defendants take issue with just over a hundred of those pages. In their supplemental expert reports, the defendants focused on 19 of the 275 cases discussed in the Larson article.[22]

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[18] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1364 (Doc. No. 193, Ex. A).

[19] See The ALFSG website, http://www.utsouthwestern.edu/labs/acute-liver/overview/. See also William Lee, M.D. Dec., May 10, 2016 at ¶ 21 (Doc. No. 220)(filed under seal); A. Larson Dep., Apr. 22, 2016 at 16 (Doc. No. 216, Ex. 6). The number of medical centers involved in the ALFSG has fluctuated between fourteen and twenty-three sites.

[20] The ALFSG is funded by the FDA through a clinical grant. This grant was later provided through a "cooperative agreement" with NIDDK/NIH. See Patricia Robuck, Ph.D., M.P.H., Dec., Mar. 16, 2016 at ¶¶ 3-4, 7 (Pl. Response to Def. Motion to Exclude, Ex. 3, under seal). See also William Lee, M.D. Dec., May 10, 2016 at ¶¶ 22, 25 (Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 23-24 (Doc. No. 216, Ex. 3); A. Larson Dep., Apr. 22, 2016 at 18 (Doc. No. 216, Ex. 6).

[21] See W. Lee Dep., Apr. 14, 2016 at 29 (Doc. No. 216, Ex. 3).

[22] Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372 (Doc. No. 193, Ex. A).

The materials produced included, among other things, case report forms (CRFs) for all 275 cases discussed in the article and spreadsheets related to the Larson article, as well as Manuals of Operations of the ALFSG governing the

The Larson article was a descriptive epidemiological study of over six hundred patients who experienced ALF at the ALFSG's twenty-two tertiary centers nationwide for a period of 6 years (from 1998 to 2003).[23] The purpose of the study was to look at incidence, risk factors, and outcomes of acetaminophen-induced ALF.[24] The study found, among other things, that 19 patients reported taking 4 grams or less of acetaminophen per day.[25] This observation was significant because it indicated that acetaminophen-induced ALF may occur at the maximum daily recommended dose of acetaminophen (4 g).[26] The article also indicated that those 19 patients more often used or abused alcohol than the other study patients.[27] The article further found that acetaminophen has a "narrow

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collection of data used for the publication of the Larson study. The defendants culled through the documents produced to find those 19 cases. They then submitted an affidavit from Dr. Lee confirming that these cases were, in fact, the 19 low-dose cases in question. The parties have provided me with a copy of the 19 low-dose case data.

[23] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1364-1366 (Doc. No. 193, Ex. A). See also William Lee, M.D. Dec., May 10, 2016 at ¶ 31 (Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 184-85 (Doc. No. 216, Ex. 3); Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶¶ 7, 22 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal).

[24] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1364-65 (Doc. No. 193, Ex. A). See also William Lee, M.D. Dec., May 10, 2016 at ¶ 14 (Doc. No. 220)(filed under seal); A. Larson Dep., Apr. 22, 2016 at 51 (Doc. No. 216, Ex. 6).

[25] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1368 (Doc. No. 193, Ex. A).

[26] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1364 (Doc. No. 193, Ex. A). The maximum daily recommended dose of acetaminophen has since been lowered to 3 grams per day.

[27] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1370 (Doc. No. 193, Ex. A)("Because the subjects with ALF reporting use of ≤4 g acetaminophen per day were often alcohol abusers (65%) and the amount of daily alcohol consumed was greater than that reported by patients who admitted to taking ≤4 g acetaminophen per day (data not shown), ethanol may still serve as an important co-factor in these lower-dose subjects.").

therapeutic margin," such that even 7.5 g/day may cause liver failure.[28] However, the article admitted that "precise information on dosing is often difficult to acquire in some of these patients."[29] The article disclosed, as is common in ALF cases, that written consent was obtained from patients' next of kin because, by definition of having ALF, the patients were considered encephalopathic (i.e., of an altered mental state).[30]

In order for ALF cases to be included in the study, patients needed to meet certain criteria: (1) a history of potentially toxic acetaminophen ingestion (i.e., >4 g/day, the maximum dose recommended on the package) within 7 days of presentation; (2) detection of any level of acetaminophen in the serum; or (3) a serum alanine aminotransferase (ALT) >1,000 IU/L with a history of acetaminophen ingestion, irrespective of the acetaminophen level.[31] Before including patients in the study, the study investigators excluded patients with competing causes of ALF, such as acute hepatitis A and B, hepatic ischemia, autoimmune hepatitis, and Wilson disease.[32]

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[28] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1370 (Doc. No. 193, Ex. A)("Our data suggest that there is a narrow therapeutic margin and that consistent use of as little as 7.5 g/day may be hazardous.").

[29] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1365 (Doc. No. 193, Ex. A).

[30] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1370 (Doc. No. 193, Ex. A).

[31] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1365 (Doc. No. 193, Ex. A). See also Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 24 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 33 (Doc. No. 220)(filed under seal).

[32] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1365 (Doc. No. 193, Ex. A). See also Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 23 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal). William Lee, M.D. Dec., May 10, 2016 at ¶ 32 (Doc. No. 220)(filed under seal).

Since its publication, the Larson article has been relied on by FDA Advisory Committees and cited by scientists and medical professionals discussing acetaminophen-induced liver injury.[33]

III. The Reliability of Defendants' Supplemental Opinions on the Larson 19 "Low-Dose" Cases

To support their motion, the defendants have submitted three supplemental reports prepared by their experts. These supplemental reports are the only evidence the defendants provide to support their motion to exclude the Larson article, beyond the data and article itself.

The plaintiff has moved to strike the defendants' supplemental expert reports under Daubert. She argues that the defense experts' opinions on the Larson article are unreliable and unhelpful. Because the defense experts' opinions are a key part of their motion to exclude the Larson article, I will first address the plaintiff's motion to strike.

A. Plaintiff's Motion to Strike Defendants' Opinions Regarding the 19 Low-Dose Cases

The defendants' supplemental expert reports all assert that the ALFSG's methodology in analyzing the 19 low-dose cases was unreliable. They support this conclusion by offering four main criticisms: 1) the patients' reported dose history is inaccurate,[34] 2) the patients' diagnosis of acetaminophen-induced ALF is inaccurate,[35] 3)

[33] See, e.g., 71 Fed. Reg. 77347 (Dec. 26, 2006)(2006 Proposed Rule on Liver Warnings)(Pl. Resp. to Mot. To Exclude, Ex. 9, filed under seal); 74 Fed. Reg. 19406 (Apr. 29, 2009)(Pl. Resp. to Mot. To Exclude, Ex. 16, filed under seal); CDER Working Group Executive Summary and Recommendations, Feb. 26, 2008 (Pl. Resp. to Mot. To Exclude, Ex. 12, filed under seal).

[34] See, e.g., J. Brent Supp. Ex. Rep., Jan. 28, 2016 at 16 (Doc. No. 193, Ex. D)("Given the patient's severe alcohol abuse, the uncertainty of her dosing history, the body burden, and the apparent use of extra acetaminophen-containing medication, this patient should not have been included in Larson et al. (2005) as a case of ALF due to

the patients had reported histories of alcohol and/or illegal drug use,[36] and 4) the patients' cases were mishandled in one way or another (i.e., the ALFSG's analysis was "sloppy").[37] Based on these criticisms, all three experts opine that *none* of the 19 cases can be considered reliable and should have been excluded from the Larson article's findings.[38] District court judges are tasked with "ensuring that an expert's testimony both

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acetaminophen ingestion of less than or equal to 4 grams per day."); S. Flamm Supp. Ex. Rep., Jan. 28, 2016 at 5 (Doc. No. 193, Ex. C)("If she did have ALF, the fact that the medication list does not match the toxicology screen, and the calculated body burden of acetaminophen of approximately 23 grams at the time ingestion, proves that the medication and dosing histories are inaccurate."); R. Brown Supp. Ex. Rep., Jan. 28, 2016 at 4 (Doc. No. 193, Ex. B)("Given her significant alcohol abuse and the absence of any information on her ingestion of any acetaminophen containing products, the acetaminophen dosing information is unreliable. The data in this CRF do not support classifying this patient as a case of acute liver failure from the ingestion of ≤ 4 grams per day of acetaminophen.").

[35] See, e.g., J. Brent Supp. Ex. Rep., Jan. 28, 2016 at 13 (Doc. No. 193, Ex. D)("Because of the uncertainty in the dose history, the inability to rule out alternative causes, and the laboratory detection of two medications not included on the medication list obtained by history, this patient should not have been included in Larson et al. (2005) as a case of ALF due to acetaminophen ingestion of less than or equal to 4 grams per day."); S. Flamm Supp. Ex. Rep., Jan. 28, 2016 at 6 (Doc. No. 193, Ex. C)("In light of her alcohol abuse and the potential presence of cirrhosis, her use of opiates and benzodiazepines, and the unreliable acetaminophen dosing history recorded on the forms, this case should not have been designated as ALF resulting from ingestion of 'low-dose' acetaminophen."); R. Brown Supp. Ex. Rep., Jan. 28, 2016 at 4 (Doc. No. 193, Ex. B)("For this case, the more likely diagnosis is liver failure secondary to hepatic ischemia.").

[36] See, e.g., J. Brent Supp. Ex. Rep., Jan. 28, 2016 at 11 (Doc. No. 193, Ex. D)("Given the clearly noted uncertainty in this patient's dosing and the history of chronic severe alcohol abuse making the history unreliable, this patient should not have been included in Larson et al. (2005) as a case of ALF due to acetaminophen ingestion of less than or equal to 4 grams per day."); S. Flamm Supp. Ex. Rep., Jan. 28, 2016 at 3 (Doc. No. 193, Ex. C)("Because an alternative cause, cocaine, was not ruled out as the etiology of the patient's condition, this case cannot confidently be classified as a case of acetaminophen-induced ALF. This case should instead have been classified as indeterminate."); R. Brown Supp. Ex. Rep., Jan. 28, 2016 at 4 (Doc. No. 193, Ex. B)("The data in this CRF do not support classifying this patient as a case of acute liver failure from the ingestion of ≤ 4 grams per day of acetaminophen, and an alternative cause of the patient's condition, cocaine use leading to hepatic ischemia, was not ruled out.").

[37] See, e.g., J. Brent Supp. Ex. Rep., Jan. 28, 2016 at 7-8 (Doc. No. 193, Ex. D)("Because there are multiple medications detected in the toxicology screen that were not reported, the patient was encephalopathic, and she had a history of alcohol abuse, a reliable dosing history was unlikely."); S. Flamm Supp. Ex. Rep., Jan. 28, 2016 at 5 (Doc. No. 193, Ex. C)("Because of the history provided by the wife that the patient overdosed, the history provided by the son that this may have been a 'suicide gesture,' the dose of Lortab listed was the 'prescribed dose' rather than the ingested dose, and the discrepancies between the medication histories and toxicology screen, this case should not have been designated ALF resulting from ingestion of 'low-dose' acetaminophen."); R. Brown Supp. Ex. Rep., Jan. 28, 2016 at 6-7 (Doc. No. 193, Ex. B)("Given the discrepant histories provided by his wife and son (which likely are more accurate), the calculated total body burden, and the inconsistencies within the data forms, the acetaminophen dosing information is unreliable and likely significantly underestimates the total dose.").

[38] See J. Brent Supp. Ex. Rep., Jan. 28, 2016 (Doc. No. 193, Ex. D); S. Flamm Supp. Ex. Rep., Jan. 28, 2016 (Doc. No. 193, Ex. C); R. Brown Supp. Ex. Rep., Jan. 28, 2016 (Doc. No. 193, Ex. B).

rests on a reliable foundation and is relevant to the task at hand." Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 597 (1993). The plaintiff challenges both the reliability of the defense experts' supplemental opinions and their relevance or "helpfulness" under Daubert.

B. Defense Experts' Dose Prediction Methodology is Unreliable[39]

The defense experts opine that the majority of the 19 cases include an inaccurate dosing history. They support this conclusion by using a two-step methodology, which they claim determines what the patients' dosing history was.[40] First, they determined the "body burden" of the patient at the time their blood sample was taken in the study. This "body burden" formula is a pharmacokinetic calculation to determine how much acetaminophen is in the bloodstream at the time blood was drawn.[41] It is sometimes used in clinical practice to help physicians determine when or how much antidote a patient may need in the event that the acetaminophen has caused liver failure.[42] This formula is

[39] For an overview of how acetaminophen is understood to cause liver toxicity, how it is treated, and more information about terms discussed in this memorandum, see L. James, Acetaminophen: Pathology and Clinical Presentation of Hepatotoxicity, Chapter 20 in Drug-Induced Liver Disease (N. Kaplowitz & L. D. Deleve, Eds.)(3rd Ed.)(2013).

[40] See J. Brent Supp. Ex. Rep., Jan. 28, 2016 at 4-5 (Doc. No. 193, Ex. D); S. Flamm Supp. Ex. Rep., Jan. 28, 2016 at 3 (Doc. No. 193, Ex. C); R. Brown Supp. Ex. Rep., Jan. 28, 2016 at 4-13 (Doc. No. 193, Ex. B). I note that Dr. Brown does not explain his methodology in this regard; he simply uses it within his analysis of the 19 cases.

[41] Pharmacokinetics is defined as the study of the time course of absorption, distribution, metabolism, and excretion of drugs. See American Society of Health-System Pharmacists, "Introduction to Pharmacokinetics and Pharmacodynamics," available at http://www.ashp.org/doclibrary/bookstore/p2418-chapter1.aspx (last visited May 6, 2016).

[42] See J. Brent Dep., Mar. 30, 2016 at 58 (Doc. No. 206, Ex. D)("Q. So that's all I'm trying to be clear about. The use of the nomogram is to determine whether n acetylcysteine should be given to a patient and can only be used reliably for a patient who's taken a single ingestion at a known time, correct? A. With the -- except in the case of the qualifier that I just mentioned. Q. I'm just talking about the use of the nomogram. A. Yes.").

more often used in research settings to understand how acetaminophen is processed and metabolized by the body.[43]

After calculating the amount of acetaminophen in the patients' bloodstream using the "body burden," the defense experts then used a "half-life" formula to calculate backwards how much acetaminophen should have been in the patients' bloodstreams at the time they reported to have taken their last ingestion of acetaminophen. The "half-life" formula is a pharmacokinetic calculation to determine the rate at which a drug is metabolized by the body.[44] In the case of acetaminophen, its half-life may vary depending on how quickly the liver is processing the acetaminophen toxins. If the liver is healthy, acetaminophen should have a half-life of two hours.[45] However, if it is damaged

[43] See S. Flamm Dep., Apr. 8, 2016 at 101 (Doc. No. 206, Ex. E)("Q. Is body burden a calculation that is routinely found in patients' medical records with acetaminophen ingestion and hepatotoxicity? A. Is it routinely found in the medical records? I would say no. Q. Is it a calculation, body burden, that is on the protocols that you all use at Northwestern? A. For some medications, yes. Q. But not for acetaminophen? A. It's not on a protocol for acetaminophen. Q. Is it -- it's not generally used, is it, in Northwestern? …A. For acetaminophen it's not generally used in clinical practice.") and at 117 (stating same). See also A. Larson Dep., Apr. 22, 2016 at 172-74 (Doc. No. 216, Ex. 6)("Q. Have you ever calculated a body burden for any drug? A. No. Q. Do you know how to? A. Yes. Q. How do you do it? A Well, I would have to look it up because I haven't used it in a long time, but it's not something normally used. Q. Normally used by who? A. By hepatologists. Q. Are there clinicians in hospitals who do calculate body burdens for drugs? A. Not that I know of. Q. You have not ever spoken to an emergency room doctor who had to calculate a body burden for a patient? A. They have never-- no…. It's been reported in literature."); S. Flamm Dep., Apr. 8, 2016 at 171-72 (Doc. No. 206, Ex. E)("Q. And your body burden was not used in 2005, even though you put it in this report now. So, this is where I am having a hard time. You've included this body burden calculation, which clearly is not used in clinical practice in scientific medicine in 2005, was it? True? A. In research setting it's used by me…. I absolutely would use this in a research setting to try to determine this. Absolutely I would."); W. Lee Dep., Apr. 14, 2016 at 202 (Doc. No. 216, Ex. 3)("Q. And does body burden tell us the amount of drug in the body following metabolism after the last dose? A. No.") and at 204 ("Q…Have you any basis to dispute the equation set forth in the Goodman and Gilman textbook for calculating body burden? A. I don't believe that it -- I think it's an oversimplification.").

[44] See S. Flamm Dep., Apr. 8, 2016 at 285-86 (Doc. No. 206, Ex. E).

[45] See A. Larson Dep., Apr. 22, 2016 at 178-79 (Doc. No. 216, Ex. 6); F. Schiodt, et al., "The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdosage," Clinical Pharmacology & Therapeutics, April 2002, 221-225, 221 (Doc. No. 206, Ex. R).

or failing, acetaminophen's half-life can be upwards of 12 to 24 hours.[46] The "half-life" calculation is also one that may be used to help physicians determine how much antidote a patient experiencing acetaminophen-induced ALF may need to be given.[47] If the half-life takes longer, this often correlates with more liver damage, hence the need for longer treatment of the antidote.[48] It is sometimes used in a clinical setting but more often used in research to understand how acetaminophen is processed.[49]

After going through these two steps, the defense experts claim that their calculations represented the amount of acetaminophen in the patients' bodies at the time they last took a dose. They claim this calculation shows that the dosing history in most of the 19 cases was above what the patients reported.

1. Reliability under Daubert

The plaintiff argues that the formula used by defense experts to predict dose—the "body burden half-life" formula"—is unreliable. They point out that this formula has never been published, tested, or used in clinical practice.

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[46] See F. Schiodt, et al., "The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdosage," Clinical Pharmacology & Therapeutics, April 2002, 221-225, 223, 224 (Doc. No. 206, Ex. R).

[47] See, e.g., F. Schiodt, et al., "The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdosage," Clinical Pharmacology & Therapeutics, April 2002, 221-225, 223 (Doc. No. 206, Ex. R).

[48] See F. Schiodt, et al., "The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdosage," Clinical Pharmacology & Therapeutics, April 2002, 221-225, 222-24 (Doc. No. 206, Ex. R).

[49] See R. Dart, B. Rumack, "Central Nervous System Agents," Acetaminophen, Sec. 8, Chap. 126, 723-738, 731 in Medical Toxicology (3rd Ed.)(2004)(Doc. No. 206, Ex. O)(explaining purpose of nonogram); S. Flamm Dep., Apr. 8, 2016 at 122 (Doc. No. 206, Ex. E)("[Determining dose is] [u]sually not important clinically. You see a patient that you think might have acetaminophen toxicity and you treat them. You treat them with N-acetylcysteine [antidote]. There is no downside to it. So, in a clinical setting it's often not germane. Where it becomes germane is more in a research setting where you're trying to ascertain question -- answer -- ascertain data and answer questions where it becomes more important.") and at 137 ("As I said earlier, in clinical practice, it doesn't matter what the dose is. It matters in research studies. [D]ose doesn't matter for that patient in clinical practice. You want to know what the diagnosis is and then you give the patient N-acetylcysteine, which is the antidote for acetaminophen.").

Under Daubert and Rule 702, an expert's opinion must be "based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation.'" In re Paoli, 35 F.3d at 742 (quoting Daubert, 509 U.S. 579, 591 (1993)). "Daubert requires the district court to act as 'gatekeeper' and to assure that the scientific methodology upon which the expert opinion is founded is reliable, i.e., that the expert's conclusion is based on good grounds (the methods and principles of science)." In re Paoli R.R. Yard PCB Litigation, 35 F.3d 717, 732 (3d Cir. 1994). "Expert evidence can be both powerful and quite misleading because of the difficulty in evaluating it." Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 595 (1993)(quoting Weinstein, Rule 702 of the Federal Rules of Evidence is Sound; It Should Not Be Amended, 138 F.R.D. 631, 632 (1991)). "Because of this risk, the judge in weighing possible prejudice against probative force under Rule 403 of the present rules exercises more control over experts than over lay witnesses." Id. (quoting Weinstein, Rule 702 of the Federal Rules of Evidence is Sound; It Should Not Be Amended, 138 F.R.D. 631, 632 (1991)).

Daubert instructed the district court to look at several factors in determining whether methodology is reliable:

1) whether it can be tested;
2) whether the theory or technique has been subjected to peer review and publication;
3) the known or potential rate of error;
4) the existence and maintenance of standards controlling the technique's operation; and

5) whether the methodology is generally accepted in the scientific community.

Daubert, 509 U.S. at 592-95. See also In re Paoli, 35 F.3d at 742 (discussing Daubert reliability factors). This inquiry is a flexible one. Id. Judges within this Circuit should also consider how and when the methodology is used outside of litigation. In re Paoli, 35 F.3d at 742 (discussing reliability factors under Daubert and Third Circuit caselaw). The proponent of the contested evidence or methodology bears the burden to show by a preponderance of the evidence that it is reliable.[50] See id. at 743-44.

2. Applying Daubert to the "Body Burden Half-life" Methodology

While the "body burden" formula and the "half-life" formula are methods which had been found to be reliable in the scientific community, there is no evidence to show that using them together to determine dosing history—as the defense experts have used them—is a reliable methodology. See In re Paoli, 35 F.3d at 748 ("If the expert's reliance on [certain data] to draw conclusions…constitutes a methodological flaw, it is a methodological 'flaw' consisting of relying on data not of a type reasonably relied upon by experts.").

This "body burden half-life" methodology is not generally accepted by the scientific community. The defendants have offered no evidence that this method has been

[50] Technically, the defendants are challenging the article as a source of information on which plaintiff's experts can rely in forming their opinions at trial. Rule 703 discusses the admissibility of the facts or data on which experts rely. See FED. R. EVID. 703 ("An expert may base an opinion on facts or data in the case that the expert has been made aware of or personally observed. If experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted. But if the facts or data would otherwise be inadmissible, the proponent of the opinion may disclose them to the jury only if their probative value in helping the jury evaluate the opinion substantially outweighs their prejudicial effect."). The reliability requirement for Rule 702 and 703 invoke the same principles and considerations. See In re Paoli, 35 F.3d at 748.

used in a clinical setting.[51] Instead, the defense experts admit that the only time they have used this "body burden half-life" methodology has been for this litigation. See In re Paoli, 35 F.3d at 742; S. Flamm Dep., Apr. 8, 2016 at 149 (Doc. No. 206, Ex. E)("[W]e don't do this in clinical practice. This is only as a result of this litigation. We don't do that kind of a thing especially with chronic ingestion."). There is no evidence that a regulatory agency, such as the FDA or NIH, has used, cited, or approved this methodology to determine dosing. [52]

There is no evidence that McNeil or Johnson & Johnson have used this methodology before in their internal research.[53] None of the defense experts have written a paper using this methodology.[54] Though Dr. Flamm and Dr. Brown are current or former members of the ALFSG, they have never presented this dosing-determinate

[51] See S. Flamm Dep., Apr. 8, 2016 at 121-22 (Doc. No. 206, Ex. E)("Q. Have you ever suggested it to your colleagues at Northwestern? A. In a clinical setting? Q. Yes. A. No. Q. And none of your colleagues use it in clinical setting, do they? A. I'm not aware that any do. Usually not important clinically. You see a patient that you think might have acetaminophen toxicity and you treat them. You treat them with N-acetylcysteine. There is no downside to it. So, in a clinical setting it's often not germane. Where it becomes germane is more in a research setting where you're trying to ascertain question -- answer -- ascertain data and answer questions where it becomes more important. Q. And -- A. So, it's more in a research setting than a clinical setting.") and at 125 ("Again, in clinical practice it's just not something you use, so it's not something that I 9 would be using on a day-to-day basis."). See also id. at 150, 182, 184.

[52] See S. Flamm Dep., Apr. 8, 2016 at 106-07 (Doc. No. 206, Ex. E.)("Q. Okay. You're not aware of the FDA ever utilizing this half-life/body burden method in order to try and calculate or confirm dose in a chronic acetaminophen dosing situation, are you? A. I'm not aware that the FDA has done it."), at 147 (same), and at 176 (same).

[53] See S. Flamm Dep., Apr. 8, 2016 at 147 (Doc. No. 206, Ex. E)("Q. And the counsel for McNeil have not provided you with any documents to demonstrate that McNeil has in fact proposed to the FDA or to anybody the use of this body burden/half-life formula that you use in your article. True?...A. True.").

[54] See S. Flamm Dep., Apr. 8, 2016 at 149 (Doc. No. 206, Ex. E). See also Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 37(d)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 48(c)(Doc. No. 220)(filed under seal).

methodology to their colleagues at the ALFSG as either a new procedure or a way to critique/test previous findings.[55] The methodology has never been tested or validated.[56]

Furthermore, the plaintiff points out why this methodology has not been used in this way: the assumption of a simple "half-life" is not appropriate for chronic dosing or multiple doses taken over multiple days.[57] If a person does take too much acetaminophen and liver failure results, the person may not realize that they are experiencing liver failure.[58] The symptoms of liver failure are often similar to those of many common illnesses.[59] As a result, ingested doses taken after the liver has failed may not be

[55] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 37(d)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 44(A), (C)(Doc. No. 220)(filed under seal); A. Larson Dep., Apr. 22, 2016 at 28-29, 36-37, 39-40, 78-79 (Doc. No. 216, Ex. 6); W. Lee Dep., Apr. 14, 2016 at 58 (Doc. No. 216, Ex. 3)("Q. Okay. At any time either before or after the Larson paper was published, did Dr. Brown ever contact you as a colleague in the normal course of his scientific endeavors to suggest that the paper was improperly done or ask you to see the data? A. No. Q. After the publication and outside of litigation, did Dr. Brown ever ask to see the Larson data so that he could look at the data himself? A. No. Q. Other than in litigation, has Dr. Brown ever criticized your research or methodology for the Larson paper in any medical or scientific form? A. No.) and at 63 ("Q. Okay. And I'm going back to Dr. Flamm and his criticism of the Acute Liver Failure Study Group. Other than in litigation as a consultant for McNeil in litigation, has Dr. Flamm ever criticized your research or methodology in any scientific or medical form? A. No. Q. Has he written any editorial in any journal questioning the conclusions of the Acute Liver Failure Study Group, including the Larson paper? A. No. Q. As an AFSLG [sic] investigator, did he ever call you to discuss any scientific criticism that he had regarding the Larson paper? A. No."); P. Robuck Dep., Apr. 18, 2016 at 20, 132, 170 (Doc. No. 216, Ex. 4); S. Flamm Dep., Apr. 8, 2016 at 122 (Doc. No. 206, Ex. E)("Q. Have you ever suggested to the Acute Liver Failure Study Group that as part of the case review form they should include your body burden/half-life calculation? A. No.").

[56] See R. Brown Dep., Apr. 20, 2016 at 294 (Pl. Motion to Strike, Ex. 6); W. Lee Dep., Apr. 14, 2016 at 56-57 (Doc. No. 216, Ex. 3); S. Flamm Dep., Apr. 8, 2016 at 102 (Doc. No. 206, Ex. E)("Q…Rumack's body burden calculation has never been validated. You've admitted that. True?...A. In studies it's never been validated.").

[57] See William Lee, M.D. Dec., May 10, 2016 at ¶ 48(c)(Doc. No. 220)(filed under seal); Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 37(c)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal).

[58] See R. Dart, B. Rumack, "Central Nervous System Agents," Acetaminophen, Sec. 8, Chap. 126, 723-738 in Medical Toxicology (3rd Ed.)(2004)(Doc. No. 206, Ex. O)("The treatment of patients with repeated administration of acetaminophen over a day or more of time is still evolving. The acetaminophen nomogram cannot be used in these cases. Emerging research suggest that patients in whom liver injury is going to develop from repeated dosing already manifest that injury at the time of presentation.").

[59] See, e.g., R. Dart, B. Rumack, "Central Nervous System Agents," Acetaminophen, Sec. 8, Chap. 126, 723-738, 730 in Medical Toxicology (3rd Ed.)(2004)(Doc. No. 206, Ex. O)(explaining how symptoms of acute overdose include abdominal pain, nausea, vomiting).

processed at all. Since it is not always clear in hindsight when the liver has failed, it is difficult for an accurate "half-life" calculation to be created for chronic dosing.

For this reason, this "half-life" formula—when it is used—is only appropriate for patients who took large amounts of a single dose (i.e., suicide attempts).[60] The literature applying "half-life" to determine dosage clearly states that this formula is only reliable for single ingestions.[61]

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[60] This methodology was based on something called the Rumack-Matthews nonogram. See S. Flamm Dep., May 5, 2015 at 265 (Pl. Motion to Strike, Ex. 1). The nomogram, however, was not intended to be used for multiple or chronic dosing. See S. Flamm Dep., Apr. 8, 2016 at 261 (Doc. No. 206, Ex. E)("Q. Who is Dr. Rumack, to your knowledge? A. Dr. Rumack is a widely-known toxicologist who has published numerous articles in acetaminophen toxicity and liver failure and in fact is the author of the Rumack nomogram, which is used for body burden analysis and when to use N-acetylcysteine in patients with acetaminophen-related hepatotoxicity after a *single-point* ingestion. Very well-known man in the field." (emphasis added)); J. Brent Dep., Mar. 30, 2016 at 57 (Doc. No. 206, Ex. D)("Q.…You would agree with that, that the Rumack nomogram cannot be used for patients taking multiple doses of acetaminophen over multiple days, correct? A. That's correct, unless -- unless the level is -- with the one exception, with the level being high based on the time since the last dose, but that's not what it's designed to do, and that's not the way we generally use it. Q. Okay. So let me try that again. You would agree that the Rumack nomogram is to be used only in patients who have taken a single-point ingestion of acetaminophen at a known time, true? A. Based on -- with the addition of that qualifier that I just gave, yes, that's true.").

See also W. Lee Dep., Apr. 14, 2016 at 210-12 (Doc. No. 216, Ex. 3)("Q. Now, who is Barry Rumack? Let's go back 7 to that Exhibit 6. A. He -- I think he started out life as a pediatrician, but he spent some time in the UK and the United -- so did I. And in the UK in those early days -- and he's -- he's an older guy, as I am -- that was where more paracetamol cases were found -- that's acetaminophen, of course. And so he studied it a bit over there, and he came up with the so-called 'Rumack nomogram.'… He published the nomogram based upon scientific data that he holds -- A. Yes. Yes. What year was that that he published the nomogram. Q. Probably in the '70s, correct? A. Yes. Q. And that nomogram that you referenced is used -- was used at UTSMC, correct? A. Not very often. Q. No? Not in the emergency room? A. That -- I don't know. I'm not an emergency room doctor. They -- they may use it more than -- more than I think. But it's not valuable very often. Q. The -- the nomogram is used when the patient's brought in -- first brought into the hospital in -- in a potential single overdose case, correct? A. Yes. And they have to be a single overdose….They have to be a single overdose and the time of ingestion has to be known. Q. And -- A. Most cases that we see do not have either the exact time of ingestion. So it -- it -- or -- or what -- and as -- as we've talked about with the unintentional cases, there's a lot of cases that are not a single time point. At least 50 percent are not a single time point. So -- so the average hepatologist doesn't have much use for the Rumack nomogram, but I'm not -- I'm not an ED doctor. I -- it may be more commonly used there. Q. In other words, there may be clinicians of other stripes who use the nomogram more than a hepatologist. Fair? A. That's correct.") and at 368-69 (discussing same).

[61] See James, et al., "Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure," Drug Metabolism and Disposition, Vol. 37, No. 8, 1779-1784, 1782 (2009)(Doc. No. 206, Ex. S)("The Rumack nomogram, based on the measurement of APAP concentrations in peripheral blood relative to the reported time of overdose, is used in the clinical setting (e.g., emergency departments) to assess the risk of developing toxicity following acute APAP overdose. It is the cornerstone of evaluation and management for patients with *single, time-point ingestions who present within 24 h of APAP overdose* (Rumack et al., 1981; Rumack, 2002). However, beyond the acute stages of APAP toxicity, or in patients with unclear histories regarding the time of the overdose or ingestions at multiple time points, the utility of the Rumack nomogram is limited." (emphasis added)).

The defense experts assume a "half-life" of 11 or 12 hours.[62] However, the literature shows that "half-life" can be highly variable and unpredictable—ranging anywhere from 2 hours to over 24 hours depending on the level of liver damage a person

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During his deposition, Dr. Flamm pointed to a paper by Dr. Barry Rumack, which he claimed used this methodology for chronic dosing. However, the paper itself clearly states the methodology was only intended to be used for single ingestions. See B. Rumack, Acetaminophen Hepatotoxicity: The First 35 Years, Clinical Toxicology, 40(1), 3-20 (2002), at 4-5 (Doc. No. 206, Ex. N)("The nomogram was only intended to guide an early clinical decision irrespective of the patient's half-life following a single acute overdose and was not intended to provide information in chronic ingestions."); S. Flamm Dep., Apr. 8, 2016 at 108-09 (Doc. No. 206, Ex. E). See also S. Flamm Dep., Apr. 8, 2016 at 261 (Doc. No. 206, Ex. E)("Q. Who is Dr. Rumack, to your knowledge? A. Dr. Rumack is a widely-known toxicologist who has published numerous articles in acetaminophen toxicity and liver failure and in fact is the author of the Rumack nomogram, which is used for body burden analysis and when to use N-acetylcysteine in patients with acetaminophen-related hepatotoxicity after a *single-point* ingestion. Very well-known man in the field." (emphasis added)).

Another article cited by Dr. Flamm also indicated that the nonogram was only intended for single doses. See R. Dart, B. Rumack, "Central Nervous System Agents," Acetaminophen, Sec. 8, Chap. 126, 723-738, 736 in Medical Toxicology (3rd Ed.)(2004)(Doc. No. 206, Ex. O)("The treatment of patients with repeated administration of acetaminophen over a day or more of time is still evolving. The acetaminophen nomogram cannot be used in these cases. Emerging research suggest that patients in whom liver injury is going to develop from repeated dosing already manifest that injury at the time of presentation.").

The third article to which Dr. Flamm points is one by C.K. Gelotte, a McNeil employee, along with several other McNeil employees. See S. Flamm Dep., Apr. 8, 2016 at 284 (Doc. No. 206, Ex. E); Gelotte, et al., "Disposition of Acetaminophen at 4, 6, and 8 g/day for 3 days in Healthy Young Adults, Clinical Pharmacology & Therapeutics, Mar. 21, 2007 (Doc. No. 206, Ex. Q). The Gelotte article, however, notes that "no nonogram exists to guide risk assessment and treatment of [] cases [involving multiple doses]." Id. at 2. The article goes on to say that the patients involved in the study accumulated less toxins in their bodies by taking at or just above the recommended dose than previously thought. Id. at 6. However, it recognized that this was "a completely novel finding." Id. Given the number of un-biased sources which recognize the limitation of the nomogram for multiple dosing, this article is not helpful.

[62] See S. Flamm Supp. Ex. Rep., Jan. 28, 2016 at 3-11 (Doc. No. 193, Ex. C); S. Flamm Dep., Apr. 8, 2016 at 273-74 (Doc. No. 206, Ex. E)("Q. And did they then publish what the range of half-lives looks like in acute liver failure from acetaminophen hepatotoxicity? A. Yes, they did. Q. And what was the range in patients with -- what was the median, let's use that, for patients with acute liver failure who survived? A. 11.2 hours. Q. And what number did you use for half-life in your supplemental expert report where you didn't have the ability to calculate an actual half-life, what number did you use as an estimate for those patients? A. 12 hours. I picked a little higher number which would bias against -- which would bias against my analysis or bias against overestimating how much a patient may have taken. Q. And is a 12-hour half-life, based upon your own clinical experience, not an unreasonable estimate for a patient who has acute liver failure due to acetaminophen hepatotoxicity? A. I think it's very reasonable, supported in the literature."); J. Brent Supp. Ex. Rep., Jan. 28, 2016 at 4-5, 9-17 (Doc. No. 193, Ex. D); J. Brent Dep., Mar. 30, 2016 at 26, 180-83 (Doc. No. 206, Ex. D)(using 11 or 12 hour half-life); R. Brown Supp. Ex. Rep., Jan. 28, 2016 at 4-13 (Doc. No. 193, Ex. B)(most often using 12 hours but at times using other half lives).

is experiencing.[63] The defense experts' assumption about half-life is speculative at best and wholly misleading at worst.

The defendants have provided no evidence that this "body burden half-life" methodology has been used to determine patient dosing where chronic dosing is involved.[64] There are no publications—peer-reviewed or otherwise—which offer the use of this methodology as a way to determine dosing history in patients taking multiple dosing.[65]

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[63] See B. Rumack, Acetaminophen Hepatotoxicity: The First 35 Years, Clinical Toxicology, 40(1), 3-20 (2002), at 7, 15 (Doc. No. 206, Ex. N)(explaining that half-life can be 2 hours for therapeutic doses but upwards of 60 hours for hepatotoxic patients); F. Schiodt, et al., "The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdosage," Clinical Pharmacology & Therapeutics, April 2002, 221-225, 222-24 (Doc. No. 206, Ex. R)(discussing how the half-life range was from .8 to 119.7 hours, explaining that survivors of ALF had half-lives ranging from 6.9 to 119.7 hours) and at 225 ("In conclusion, our study showed that the acetaminophen half-life is well correlated with the degree of liver damage in patients treated with *N*-acetylcysteine and that the most prolonged half-lives were observed in patients with acute liver failure.").

See also W. Lee Dep., Apr. 14, 2016 at 221-23 (Doc. No. 216, Ex. 3)(explaining the variability of the half-life) and at 227 ("A. Yes. The only comment I wanted to make is that in the Schiodt paper, the range of half-lives of the ALF patients is from five hours to 87 and 119 hours. So anytime you make an assumption of 12 hours, that's a specific assumption. The median was actually 20 -- nearer to 20 hours for the acetaminophen half-life. So it's variable and unpredictable."); A. Larson Dep., Apr. 22, 2016 at 181 (Doc. No. 216, Ex. 6)("Q…Is the use of a 12-hour half-life, as an estimate for acetaminophen half-life, in an acute liver failure patient, a reasonable estimate in light of the data in [the Schiodt] study?...A: No. Q Why is that? A Because it ranged from 11 to 26, depending on whether they survived or not.").

[64] See S. Flamm Dep., Apr. 8, 2016 at 102 (Doc. No. 206, Ex. E)("Q…Rumack's body burden calculation has never been validated. You've admitted that. True?...A. In studies it's never been validated. Q. Right. And it's never been used by any of the hepatologists or the pharmacologists with respect to acetaminophen chronic dosing. True? A. I don't know. In a research setting I would use it."). Dr. Brent claims that it is used "all the time" in the case of chronic dosing for acetaminophen. See J. Brent Dep., Mar. 30, 2016 at 174-77 (Doc. No. 206, Ex. D). However, he is unable to point to any article which states this methodology is common practice for acetaminophen-induced ALF.

[65] See S. Flamm Dep., Apr. 8, 2016 at 102 (Doc. No. 206, Ex. E)("Q. Did you cite in your report to any references in the peer-reviewed medical literature for the use of this formula in the context of patients who had ingested acetaminophen multiple times and presented in acute liver failure? A. I made no citations at all in this report."), at 146 ("Q. Has that study ever been validated in clinical medicine or science as a predictor of dose in a chronic dosing situation?...A. I mean the concept of body burden and repeated dosing has been discussed in many articles. But I have not seen validation of that particular issue in acetaminophen in a study."), at 162 (same), and at 172-73 (same); J. Brent Dep., Mar. 30, 2016 at 58 (Doc. No. 206, Ex. D)("Q. Okay. But it isn't an article where 9 they were estimating body burden as you did in your supplemental expert report? A. It's the same concept. Obviously, they weren't doing it for exactly the same reason, so no, but it's the same concept. Q. Actually, in that article, they didn't have to estimate dose because they monitored the dose? A. That's correct. Q. So that's not at all what you did in your supplemental report, correct? A. Right. But it's the same concept of using body burden that way.").

Lastly, the defense experts fail to account for the inconsistent result of their "body burden half-life" formula in one low-dose case in which the patient was hospitalized while receiving acetaminophen.[66] Patient 12-010 was hospitalized for several days. During that time she was administered 12 grams or so of an opiate/acetaminophen combination (Vicodin ES) at a dose of less than 4 grams/day.[67] This dosing in a hospital setting—by a third-party carefully monitoring the patient—is a situation in which accurate dosing would be expected.[68] Nonetheless, this patient developed ALF and was transferred from that local hospital on the sixth day to Washington University in St. Louis to receive a liver transplant. The patient's liver was biopsied and showed drug toxicity. The Larson article investigators determined the cause of the ALF to be acetaminophen only. Despite all of this, all three defense experts still opine that the dosing history for this patient was unreliable based on their dubious "body burden half-life" calculations.

The defendants have the burden to show their experts' methodology is reliable.[69] The defendants have not met that burden in regards to the "body burden half-life"

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[66] See W. Lee Dep., Apr. 14, 2016 at 363-65 (Doc. No. 216, Ex. 3)(discussing hospital case and adduct/dose correlation); Anne Larson, M.D. Dec., Mar. 17, 2016 at 11 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal)(same); William Lee, M.D. Dec., May 10, 2016 at 26-27 (Doc. No. 220)(filed under seal).

[67] See A. Larson Dep., Apr. 22, 2016 at 91-93 (Doc. No. 216, Ex. 6)(discussing hospital case).

[68] See J. Brent Supp. Ex. Rep., Jan. 28, 2016 at 4 (Doc. No. 193, Ex. D)("Hence, reports about dose should be presumed unreliable unless they are obtained from a reliable source, such as a primary care giver who can document the quantity, frequency, and size of the pills or tablets taken.").

[69] My decision to exclude the defense experts' opinions is based on the fact that they have not met their burden under Daubert to show these opinions are reliable and/or helpful. However, I note where the plaintiff also offers testimony by their experts and members of the ALFSG—who are experts in acetaminophen-induced liver injury—that this combined "body burden half-life" methodology has not been used, published, or tested. See William Lee, M.D. Dec., May 10, 2016 at ¶ 48(c)(Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 105-113 (Doc. No. 216, Ex. 3); A. Larson Dep., Apr. 22, 2016 at 76-78 (Doc. No. 216, Ex. 6)("Q In a case where people take multiple doses over multiple days, is that, in your experience, a valid methodology for estimating overdose? A No, it

methodology used by its experts. In fact, this methodology is unreliable.[70] Defendants' expert opinions about dose history will be excluded.

C. Defense Experts' Opinions on Flaws in Larson Methodology Would Not be Helpful to the Jury[71]

The plaintiff also argues that the defense experts' opinions on the 19 cases would not be "helpful" to the jury. Rule 702 requires that an expert opinion may be used "[i]f scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue." FED. R. EVID. 702.

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is not. Q Why? A I believe that that was designed for single-dose calculations."). See also N. Kaplowitz Supp. Ex. Report at 5-6, Mar. 18, 2016 (Pl. Motion to Strike, Ex. 8); A. Larson Dec. at ¶37(d)(Pl. Motion to Strike, Ex. 9)("I have not seen the calculation employed by McNeil's experts used in any peer-reviewed article to calculate the chronic dose taken by a patient."); T. Davern Supp. Ex. Report, Mar. 18, 2016 at 8 (Pl. Motion to Strike, Ex. 10)("The McNeil experts frequently used calculations of the body burden of acetaminophen to discredit the estimates of acetaminophen dosing in the CRFs. These calculations make several assumptions, are overly simplistic, and have not been validated for patients with multiple timepoint/staggered ingestions and with liver failure."); L Plunkett Supp. Ex. Report, Mar. 15, 2016 (Pl. Motion to Strike, Ex. 11); R. Tackett Report, Mar. 18, 2016 (Pl. Motion to Strike, Ex. 12).

[70] The plaintiff also questions defendants' methodology regarding their post-hoc diagnosis of the 19 cases. She argues that the defense experts' failure to request adduct testing results on the 19 cases is a flaw in their methodology, rendering it unreliable. See William Lee, M.D. Dec., May 10, 2016 at ¶ 48(d)(Doc. No. 220)(filed under seal)("Neither McNeil, nor its experts, requested acetaminophen adduct data from the ALFSG before issuing their reports on the 19 low-dose Larson patients, even though this is a widely accepted test for acetaminophen causation and we have published that most of our patients have undergone such testing."); W. Lee Dep., Apr. 14, 2016 at 116 (Doc. No. 216, Ex. 3).

This adduct testing is a common procedure in establishing acetaminophen as the cause of liver injury. See S. Flamm Dep., Apr. 8, 2016 at 89 (Doc. No. 206, Ex. E.)("Q. And the assays are now considered to be the gold standard for acetaminophen causation as it relates to acute liver failure. True?... A. Yes."); William Lee, M.D. Dec., May 10, 2016 at ¶ 48(d)(Doc. No. 220)(filed under seal); A. Larson Dep., Apr. 22, 2016 at 46 (Doc. No. 216, Ex. 6).

The plaintiff has a valid point. However, I will not exclude the defendants' diagnosis analysis on this basis alone. As I explain below, the defendants' post-hoc diagnosis analysis should be excluded under Daubert more so because it is not helpful and/or confusing.

[71] The plaintiff also points out that Dr. Brown, who was asked to leave ALFSG, has irreconcilable bias. See Patricia Robuck, Ph.D., M.P.H., Dec., Mar. 16, 2016 at ¶ 12 (Pl. Response to Def. Motion to Exclude, Ex. 3, under seal); P. Robuck Dep., Apr. 18, 2016 at 130-31 (Doc. No. 216, Ex. 4); William Lee, M.D. Dec., May 10, 2016 at ¶ 44(A) (Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 56-57, 381-82 (Doc. No. 216, Ex. 3)(discussing Dr. Brown's departure from the ALFSG); A. Larson Dep., Apr. 22, 2016 at 36-37 (Doc. No. 216, Ex. 6). I do not see this fact disqualifying him from rendering an opinion on the work of the ALFSG. However, this point is most certainly appropriate for the plaintiff to bring out on cross-examination of Dr. Brown and for the jury to hear, if appropriate.

The Larson article acknowledges the limitations or "failings" identified by the defendants' experts' critiques. The article clearly states that patients' reported dosing histories may be inaccurate. The article clearly indicates that the majority of the 19 cases involved use or abuse of alcohol. The defense experts' critiques in these respects offer nothing additional to the evidence in the record. In examining whether the plaintiff's expert opinions are valid, the court, in deciding its Daubert motions, can look at the plain language of the Larson article.[72] No supplemental expert report is needed. If plaintiff's experts are permitted to testify about this subject, the defendants can easily cross-examine those experts using the article itself. If Dr. Lee or Dr. Larson is called to testify as a third-party fact witness, the defendants can use the article and its underlying data to cross-examine them on any flaws in their conclusions and methodology. Offering the defense experts' opinions on this point simply adds an unnecessary layer that could confuse the issue.

Next, the plaintiff argues that the defense experts' opinions on alternate diagnoses are not helpful. I agree. The defense experts do not opine that the ALFSG's diagnosis procedures were flawed or that the Larson article authors did not rule out alternate

[72] The critique that dose histories may be inaccurate or incomplete is not a new point. See, e.g., R. Dart, B. Rumack, "Central Nervous System Agents," Acetaminophen, Sec. 8, Chap. 126, 723-738, 729 in Medical Toxicology (3rd Ed.)(2004)(Doc. No. 206, Ex. O)(explaining why retrospective reports often find therapeutic doses of acetaminophen causing liver injury while prospective studies do not find the same, noting that the difference is "inadequate, incomplete, or frankly conflicting data" and how other literature has noted this as well); Davern, et al., Measurement of Serum Acetaminophen-Protein Adducts in Patients with Acute Liver Failure, Gastroenterology 2006: 130: 687-694, 687 (discussing how in intentional acetaminophen overdose cases patients may not recall how much they took) and at 691 ("However, those overdose patients with the most severe injury and the poorest prognoses (typically unintentional cases) present late for medical care when acetaminophen levels are often undetectable and a reliable history may not be obtained owing to altered mentation."). See also J. Brent Supp. Ex. Rep., Jan. 28, 2016 at 3 (Doc. No. 193, Ex. D)("The problem of unreliable dose histories has been widely noted and discussed in the medical literature, as described in published articles cited, with full references, in my earlier reports.").

causes. An opinion of this sort would be helpful if it showed that the methodology used to diagnosis patients included a flaw, that was not disclosed in the article or that was only apparent in seeing the raw data. This is not the opinion defense experts offer.[73]

"The judge should only exclude the evidence if the flaw is large enough that the expert lacks 'good grounds' for his or her conclusions." In re Paoli, 35 F.3d at 746. The defendants have pointed out no flaw in methodology large enough to warrant the exclusion of the Larson article.

Instead, the defense experts simply review the patients' case report forms and draw their own conclusions on what the patients' diagnoses should have been.[74] Diagnosis is imprecise and imperfect.[75] Medical experts disagree all the time about the cause of a patient's condition. Anyone analyzing a case post-hoc will be able to find errors and question a diagnosis after-the-fact.

When the defense experts do address the validity of the Larson article's methodology, they simply nit-pick the data. They do not find any overarching

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[73] Any points the defense experts do make about the ALFSG researchers' methodology in terms of diagnosis are speculative. As I explain below, the plaintiff offers evidence of what the researchers did do to rule out alternate causes. In doing so, the plaintiff meets her burden in showing that the article's methodology in this respect is reliable.

[74] See J. Brent Dep., Mar. 30, 2016 at 26, 186 (Doc. No. 206, Ex. D)("Q. Did you perform a posthoc analysis of the Larson 2005 low-dose data? A. No, I didn't do any analysis. I just took the information that was there and commented on it.").

[75] See J. Brent Dep., Mar. 30, 2016 at 139 (Doc. No. 206, Ex. D)("Q. So in the day-to-day practice of real medicine, when a physician has a patient and is trying to determine whether or not their liver failure is caused by acetaminophen, they're using an accepted methodology known as differential diagnosis; is that fair? A. Accepted in medicine, although there is no degree of certainty implicit in this concept of differential diagnosis. It's basically making your best opinion based on the evidence you have. Now, you know, is that -- diagnoses are wrong all the time, and the reason for that is because it's basically an anecdotal experiment. And so, you know, sometimes diagnoses are made with a fairly high degree of certainty if it's based on good data. Other times it's highly, highly speculative. But that's what you have to do in medicine.").

inconsistency in the Larson methodology or some pattern that only a scientist might understand as flawed.[76] Instead, they look at the forms, interpret notations negatively, and conclude from various "inconsistencies" that all the data in the case forms must be flawed.[77] In drawing these conclusions, however, they do nothing more than a facial review of the case forms. There is nothing scientific about this process; no scientific

[76] Dr. Flamm even admits that he is not criticizing the standard ALFSG criteria used in the Larson paper. See S. Flamm Dep., Apr. 8, 2016 at 96-97 (Doc. No. 206, Ex. E.)("Q. Let me ask you this. You say Larson's criteria. Do you have any basis upon which to say Anne Larson created the case report forms? A. Larson, et al. The paper's criteria. Not the case report form criteria. The paper --the criteria there in Larson, et al., not Larson's. I should be specific. Thank you for correcting that. It wasn't Larson's criteria. It was the ALFSG criteria that Larson's paper described in the methodology. Q. Well, the ALFSG's criteria is set forth in the ALFSG manuals. True? A. Yeah, same criteria. Q. And the ALFSG manuals you know were put together collaboratively by the institutions that are involved. True? A. I'm not criticizing the criteria. What I'm explaining to you -- I'm not criticizing the criteria at all."), at 187-88 ("Q. Let's be clear. There is no separate criteria for the Larson paper. The Larson paper is using ALFSG -- A. The ALFSG criteria. Q. Thank you. Which you're a principal investigator of? A. Right. What's that have to do with it? Q. It has to do with it's your organization whose criteria is being used….A. I -- there is nothing wrong with the criteria."), and at 192 ("A. There is nothing wrong with the protocol. The protocol is fine. The analysis of the case report forms is a problem. The protocol was excellent. It passed peer review. It's excellent. I don't disagree with the -- I told you at the beginning. I will tell you again. The methodology is fine, the way the study was set up. My problem is with the analysis of the case report forms. Not anything wrong with the methodology."). He admits that Dr. Larson's methodologies—her criteria for inclusion in the study, her criteria for diagnosis, and her admission in the paper itself that dosing histories are difficult to obtain—are all "good science." See S. Flamm Dep., Apr. 8, 2016 at 183-84.

[77] The alleged "inconsistencies" include: noting that the "Medications list" (question 18) question on the form does not include an acetaminophen product while the "acetaminophen specific question" (question 19) identifies an acetaminophen product; pointing out that doses noted in the indications section and the acetaminophen section were not the same; highlighting how the patient's reported dose differs from that which his/her family reported; questioning the use of a circled "?" on some forms; noting that there was different handwriting on the forms; or pointing out that information may have been entered at different times.

As explained further below, notations or corrections made in the data were instead evidence that the ALFSG researchers were re-reviewing and double checking data—an indicia of reliable methods, not sloppy ones. See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 38 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal)("The '?' on Question 2 of the Admission form was incorrectly interpreted as my doubting the dose. Anything on the form with a 'circle' or a 'circle' with a '?' means to double-check or 'query' the information in the form against the medical records and correct if necessary. I did that and confirmed the dose."); William Lee, M.D. Dec., May 10, 2016 at ¶ 17 (Doc. No. 220)(filed under seal)("The '?' on Question 2 of the Admission form was incorrectly interpreted by McNeil's experts as the Investigator doubting the dose. Anything on the form with a 'circle' or a 'circle' with a '?' means a double-check or 'query' the information in the form against the medical records and correct if necessary. By way of example, there is a '?' with a 'circle' in Question 20 [of one case form] regarding the patient's height and the note was corrected to reflect cm's instead of inches."). See also A. Larson Dep., Apr. 22, 2016 at 105-06 (Doc. No. 216, Ex. 6)(discussing this notation); William Lee, M.D. Dec., May 10, 2016 at Exs. 7 and 8 (Doc. No. 220)(filed under seal)(examples of query forms).

expertise needed in rendering their "sloppy work" conclusions.[78] I can just as easily review the data in this way and draw my own conclusions about its reliability (as I do below).

A jury can just as easily determine how much weight to give this data if these facial "inconsistencies" are brought out on cross-examination of the Larson article authors.[79] No "expert" opinion is necessary in this regard. These opinions are not helpful.

D. The Defense Experts' Supplemental Opinions Would Also Be Misleading and/or Confusing

The defense experts' opinions about the diagnosis of the 19 low-dose cases will likely be misleading, confusing, or overwhelming to the jury. See In re Paoli, 35 F.3d at 746-47; Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 595 (1993)("Because of this risk, the judge in weighing possible prejudice against probative force under Rule 403 of the present rules exercises more control over experts than over lay witnesses." (quoting Weinstein, Rule 702 of the Federal Rules of Evidence is Sound; It Should Not Be Amended, 138 F.R.D. 631, 632 (1991)); FED. R. EVID. 403 ("The court may exclude relevant evidence if its probative value is substantially outweighed by a danger of one or more of the following: unfair prejudice, confusing the issues, misleading the jury, undue delay, wasting time, or needlessly presenting cumulative evidence."). While the methodology itself isn't necessarily complex, jurors likely will be given the

[78] See S. Flamm Dep., Apr. 8, 2016 at 161 ("A….It's very to me inaccurate or --inaccurate is the wrong word. It's very sloppy to me.")(regarding whether certain medications were listed in one area of the case report form as opposed to another area), at 166 (again describing the handling of the 19 cases as "sloppy"), and at 189 (same); J. Brent Dep., Mar. 30, 2016 at 142-43 (Doc. No. 206, Ex. D)(describing the analysis as "shoddy").

[79] As explained below, the Larson article authors address these facial critiques. Their rebuttals offer plausible explanations for any seeming difference in notations, etc.

impression that this sort of post-hoc analysis of data at trial is common and permissible.[80] They may give more weight to it than it deserves. See Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 595 (1993)("Expert evidence can be both powerful and quite misleading because of the difficulty in evaluating it."); In re Paoli, 35 F.3d at 746-47.

The defendants' proposed expert testimony creates a risk that the trial will focus on the side-issue of whether the Larson article is valid. The minimal probative value it may offer would be substantially outweighed by the potential confusion or undue delay it would cause. If the validity of the Larson article is featured at trial, the plaintiff will likely then put on rebuttal evidence and testimony about the defendants' experts' methods, with the defendants then countering with their own rebuttal evidence. This situation will create (and, in fact, already has created) a trial within a trial.[81] The weaknesses of the Larson article can be explored through cross-examination of Dr. Lee, Dr. Davern, or any other authors of the article who will testify at trial. "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 586 (1993). The defendants were, in fact, permitted to get the ALFSG data for this very reason—to cross-

[80] I note that a motion to exclude a 10-year-old peer-reviewed article based on later-obtained raw data is rare. I have found no analogous decision on such a motion in my research and the parties do not cite one either.

[81] See, e.g., Sarin v. Poojan, Inc., No. 3:08-cv-1077, 2010 WL 5463250, at *6 (M.D. Pa. Dec. 29, 2010)(noting that if disputed evidence is allowed, "it will be a sideshow that distracts the jury and lengthens the trial"); Kirby v. J.C. Penney Corp., No. 2:08-cv-1088, 2009 WL 3572494, at *3 (W.D. Pa. Oct. 26, 2009)("Time devoted to either justifying or refuting the conclusions of the EEOC made in the spring of 2008 would be nothing more than the proverbial trial within a trial, requiring undue delay, waste of time, and the needless presentation of cumulative Evidence.").

examine Dr. Lee—*not* to assert a Daubert and evidentiary challenge to the Larson article or ALFSG's work generally.

The defense experts' recent post-hoc analysis of the 19 low-dose case forms would likely be misleading. The defense experts make assumptions about notations in the patient records, which are not necessarily true. For example, they assume that the notation of a circled question mark indicates an inaccurate dose. Yet, they have no basis for this assumption. Instead, this notation served as a reminder to study investigators and/or authors to double-check that a record was accurate. By all accounts, the data was double-checked. The article's authors, who do have knowledge of what those notations mean, could just as easily be asked about them on cross-examination without any speculation or misinterpretation.

For these reasons, the defendants' supplemental opinions on the Larson article will be excluded under Daubert, Rule 702, Rule 703, and Rule 403.[82]

[82] The defense experts' opinions that the Larson article would not have passed peer-review or been published if the reviewers had seen the 19 low-dose case data will also be excluded. The defense experts provide no valid basis for this opinion. It is purely speculative. To the contrary, Dr. Flamm admits that reviewers typically do not receive case reports or raw data when they peer-review an article. See S. Flamm Dep., Apr. 8, 2016 at 33 (Doc. No. 206, Ex. E)("A. This is the first time I've ever received case report forms from any published paper to review."), at 35 ("A. This is the first time I've ever received case report forms in any part of my life. And so, yes, this is the first time I've had the opportunity to write such a report."), and at 76 ("A. I have never been provided case report forms."), and at 247 ("A. When you -- I've been a peer reviewer for all 20 years since I've been here for journals, including New England Journal of Medicine and the Annals of Internal Medicine, you know, important journals. And what happens is you get a paper and that's all you get. You get a paper and you're asked to comment on it and you criticize it. You either accept or reject it or accept it with modifications. And the way you analyze that paper is you analyze the methodology, you analyze the results. You analyze the way the discussion is carried out and the conclusions that the authors make. What you never -- I've never received once, despite having done this hundreds of times, any case report forms. That is taken as a given that the analysis of the case report forms are done with high quality. So, you can criticize the methodology very accurately because it's written there. You can criticize the way the results are reported and analyzed and the discussion is carried out. But you really can't -- you don't have access to the primary data. That is a matter of, in a way, trust from the site [sic] that is or the authors or the group of people that are writing the paper.").

IV. Defendants' Motion to Exclude Use of the Larson Article

This does not end the analysis. The defendants have challenged the validity of the Larson article. The plaintiff now bears the burden of showing its reliability. See In re Paoli, 35 F.3d at 743-44. On its face, the Larson article already has numerous indicia of being a reliable source:

1) It was conducted prior to and outside this litigation;[83]

2) Its methodology and criteria for case inclusion were peer-reviewed and approved through a grant by the NIH and the NIDDK;[84]

3) It was peer-reviewed before publication by autonomous scientists from a well-known medical journal on hepatology (the study of the liver);[85]

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[83] The Larson article was also designed with input and data from Drs. Brown and Flamm, members of the ALFSG who curiously deferred their "criticisms" until they became involved as paid experts in this case. See In re Paoli, 35 F.3d at 742 (explaining how opinions made only for the purpose of litigation are given less weight in admissibility analysis by the court).

[84] This is standard criteria for ALFSG studies. See https://www.niddkrepository.org/studies/aalf/ (stating "Eligibility criteria for patients with ALF include: Altered mentation of any degree (encephalopathy); Evidence of moderately severe coagulopathy (INR ≥ 1.5); Presumed acute illness onset of less than 26 weeks; Informed consent from patient's next of kin); Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 37(a)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶¶ 34, 48(a) (Doc. No. 220)(filed under seal). See also P. Robuck Dep., Apr. 18, 2016 at 116-26, 140 (Doc. No. 216, Ex. 4).

[85] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 25 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 64 (Doc. No. 216, Ex. 6). The defendants downplay the fact that the Larson article was peer-reviewed and published. They claim that this process would be unable to detect the errors in procedure they have found because the peer-reviewers were not privy to the raw data underlying the Larson article. However, as Dr. Flamm admitted, the peer-review process typically does not involve a review of raw data. See S. Flamm Dep., Apr. 8, 2016 at 33 (Doc. No. 206, Ex. E)("A. This is the first time I've ever received case report forms from any published paper to review."), at 35 ("A. This is the first time I've ever received case report forms in any part of my life. And so, yes, this is the first time I've had the opportunity to write such a report."), and at 76 ("A. I have never been provided case report forms."), and at 247 ("A. When you -- I've been a peer reviewer for all 20 years since I've been here for journals, including New England Journal of Medicine and the Annals of Internal Medicine, you know, important journals. And what happens is you get a paper and that's all you get. You get a paper and you're asked to comment on it and you criticize it. You either accept or reject it or accept it with modifications. And the way you analyze that paper is you analyze the methodology, you analyze the results. You analyze the way the discussion is carried out and the conclusions that the authors make. What you never -- I've never received once, despite having done this hundreds of times, any case report forms. That is taken as a given that the analysis of the case report forms are done with high quality. So, you can criticize the methodology very accurately because it's written there. You can criticize the way the results are reported and analyzed and the discussion is carried out. But you really can't -- you don't have access to the primary data. That is a matter of, in a way, trust from the site that is or the authors or the group of people that are writing the paper.").

4) It was also peer-reviewed by the NIDDK/NIH;[86]

5) After publication, it was widely vetted, accepted, and cited by regulatory agencies such as the FDA and the medical community;[87] and

6) No other members of the medical or scientific community have publicly criticized its design or execution since it was published over a decade ago.[88]

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[86] The ALFSG is funded by the FDA through a clinical grant and cooperative agreement with the NIDDK/NIH. This grant was peer-reviewed. As part of this review process, a project officer for the FDA/NIH would perform site visits to review data, case report forms, standard operating procedures, and manuals of operation, among other things. In addition, an NIH scientist oversaw and critiqued the science of the ALFSG's activities. NIH also appointed an independent "Data Safety Monitoring Board" for ALFSG, which independently and confidentially reviewed the data generated by the ALFSG. At ALFSG Steering Committee meetings (a group separate from the Data Safety Monitoring Board), officers from the FDA/NIH were often present and could ask Dr. Lee questions on individual casa data being presented. ALFSG's data was also audited by the NIH and the FDA, to ensure that the information collected by the case report forms was properly transcribed into data collection spreadsheets. The NIH reviewed publications put out by the ALFSG as well, because the group was grant funded. See Patricia Robuck, Ph.D., M.P.H. Dec., Mar. 16, 2016 at ¶¶ 3-4, 7-10, 12, 14-15 (Pl. Response to Def. Motion to Exclude, Ex. 3, under seal); P. Robuck Dep., Apr. 18, 2016 at 21, 31-33, 42, 57-60, 91, 103-04, 116-21, 123-28 (Doc. No. 216, Ex. 4). See also William Lee, M.D. Dec., May 10, 2016 at ¶ 25 (Doc. No. 220)(filed under seal); W. Lee Dep. at 24 (Doc. 216, Ex. 3)("Q. How often does NIH review the grant for Acute Liver Failure Study Groups? A. We have, basically in the last three cycles, gotten five years of funding, so we have to go back every five years for renewal. Q. And when you go back, is it a process that you have to submit a lot of substantive information to get refunded? A. There's several steps. You have to go through an external advisory committee to the NIH that reviews what you've performed to date even before you're allowed to submit a grant. And then once you submit the grant, it undergoes a second review, again, by independent investigators with some expertise in the area, but no obvious conflicts of interest with us. And then they give a recommendation to the NIH. Q. Okay. So it's a -- would it be fair to say that it's basically a peer reviewed process of your entire program? A. Yes."); A. Larson Dep., Apr. 22, 2016 at 18-19 (Doc. No. 216, Ex. 6).

[87] See, e.g., 71 Fed. Reg. 77347 (Dec. 26, 2006)(2006 Proposed Rule on Liver Warnings)(Pl. Resp. to Mot. To Exclude, Ex. 9, filed under seal); 74 Fed. Reg. 19406 (Apr. 29, 2009)(Pl. Resp. to Mot. To Exclude, Ex. 16, filed under seal); CDER Working Group Executive Summary and Recommendations, Feb. 26, 2008 (Pl. Resp. to Mot. To Exclude, Ex. 12, filed under seal). While it is true that publication does not correlate with reliability, "submission to the scrutiny of the scientific community is a component of 'good science,' in part because it increases the likelihood that substantive flaws in methodology will be detected." Daubert, 509 U.S. at 593.

The fact that the Larson article has been funded, cited, and relied upon by the FDA and its advisory committees/groups gives a further nod to its inherent reliability. See Ambrosini v. Labarraque, 101 F.3d 129, 138-139 (D.C. Cir. 1996)(explaining how expert's testimony before the FDA was an indication that his methods were considered scientifically valid); Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1215 n. 20 (10th Cir. 2002) (explaining how typically the review of a study by an agency is often more rigorous than simply peer-review).

[88] See W. Lee Dep., Apr. 14, 2016 at 64-65 (Doc. No. 216, Ex. 3)("Q. Now, you mentioned before that the NIH and the FDA had funded the work of the Acute Liver Failure Study Group. Did the -- you mentioned that the FDA asked you to present data from the Acute Liver Failure Study Group in 2010 to 2009 to its advisory committee, is that true? A. That's correct. Q. Okay. At any time did any FDA scientist or medical professional ever criticize the work of the Acute Liver Failure Study Group or in particular the Larson paper? A. No. Q. At any time in the past 20 years, has the -- any scientist or medical professional at the National Institutes of Health or the United States Food and Drug Administration criticized the work of the ASFLG [sic] in general? A. ALFSG. Q. ALFSG. A. No."); A. Larson Dep., Apr. 22, 2016 at 20-21, 28-29, 64 (Doc. No. 216, Ex. 6).

See Daubert, 509 U.S. at 592-95 (offering the reliability factors); In re Paoli, 35 F.3d at 742 (discussing Daubert reliability factors).

Beyond their expert opinions (which are not admissible), the defendants rely on arguments under Daubert or the Federal Rules of Evidence. They offer the same points which their experts make—that the collection of the ALFSG data was "sloppy."[89] They essentially do a facial review of the ALFSG data and point out its flaws.

In response to the defendants' motion to exclude the Larson article, the plaintiff offered her own evidence to rebut any contentions that its methodology was flawed:

- A declaration by Dr. Lee;[90]

Dr. Flamm admitted this during his deposition. See S. Flamm Dep., Apr. 8, 2016 at 33-35(Doc. No. 206, Ex. E)(discussing how Dr. Flamm himself did not question the methodology), at 71-2 ("Q. And to your knowledge, the FDA has never questioned the integrity of the collection – the integrity of the collection or the analysis of the Acute Liver Failure Group's data, have they? A. To my knowledge, they have not. Q. Are you aware of anyone in the world besides you and another physician hired by McNeil, or a couple of physicians, who have ever criticized these physicians who published the article that is Flamm 3?...A. Yes, I was going to say that myself. I haven't criticized any physicians. I criticized the review of 19 case report forms. And I am unaware that anybody else in the world has done that.").

Most telling is that, Dr. Flamm, who was an investigator for ALFSG, saw no glaring flaws in the methodology to warrant his review of the case reports. See S. Flamm Dep., Apr. 8, 2016 at 35 (Doc. No. 206, Ex. E)("Q. And at any of those times did you reach out to your organization, the AASLD or the Acute Liver Failure Study Group, and say, 'I'd like to see the case report forms because I want to make sure this is accurate'? A. I would have absolutely no reason to do that and because I would assume that they were reviewed in -- with high-quality fashion. I've been an author on, as I told you, 40 or 50 articles and I have been an author so I have received the manuscripts like this ahead of time. There has never been a time that I have thought that I need to actually contact the people writing the article that submitted it to me to actually double-check or triple-check the case reports.") and 36 ("Q. You, from 2005 when this article was published until 2015, never raised with any of the authors of Exhibit 3 a concern that their methodology or their analysis was -- might be incorrect, did you? A. I would have no reason to even suspect it.").

[89] The defendants' oral argument was not focused on their own experts' supplemental opinions. Instead, they sought to discredit statements made by Drs. Lee, Larson, and Robuck and to point out facial errors on the Larson case reports.

[90] The defendants filed a separate motion to strike Dr. Lee's declaration. See Doc. No. 214. I denied this motion. See Doc. No. 221. See also U.S. v. Rocky Mountain Holdings, Inc., 782 F. Supp. 2d 106, 115 (E.D. Pa. 2011)("[M]otions to strike are disfavored and usually will be denied 'unless the allegations have no possible relation

- A declaration by Dr. Larson; and

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to the controversy and may cause prejudice to one of the parties, or if the allegations confuse the issues in the case.'" (internal citations omitted)).

Dr. Lee's attorney voluntarily disclosed during his deposition that there were two errors in his declaration: 1) he used the word "median" instead of "mean" in paragraph 14; and 2) he conceded that paragraph 41, which stated that the FDA had seen the 19 low-dose case forms, should have been removed during final edits. See W. Lee Dep., Apr. 14, 2016 at 155-60 (Doc. No. 216, Ex. 3)(disclosing errors in declaration). I granted the plaintiff leave to file an amended declaration on behalf of Dr. Lee to correct these two errors. See Doc. No. 219; William Lee, M.D. Dec., May 10, 2016 (Doc. No. 220)(filed under seal). The filing of the amended/corrected declaration mooted the defendants' argument on this point.

The defendants also argued that the declaration should be striken because it was drafted by plaintiff's counsel and then adopted by Dr. Lee. There was nothing untoward about the procedure used to prepare Dr. Lee's affidavit. See Walker v. George Koch Sons, Inc., No. 2:07cv274 KS–MTP, 2008 WL 4371372, at *5 (S.D. Miss. Sept. 18, 2008)(explaining how affidavits are generally prepared by counsel and then reviewed by affiants as part of litigation); Ford Motor Co. v. Edgewood Properties, Inc., 257 F.R.D. 418, 422 (D.N.J. 2009)(explaining how attorneys often prepare affidavits for third-party fact witnesses). In fact, the defendants themselves used a similar process when they prepared another declaration by Dr. Lee on the ALFSG data. See Doc. No. 215, Ex. C.

As Dr. Lee testified at his deposition, plaintiff's counsel contacted him through his attorneys, when the defendants filed their ALFSG motion on January 29, 2016. At Dr. Lee's and his attorney's request, the plaintiff's counsel sent his attorneys the supplemental reports of defense experts. Dr. Lee reviewed these materials and re-reviewed the ALFSG data. After conducting his own investigation and independent review of the reports, Dr. Lee met with plaintiff's counsel, Christopher Tisi, Esq. and William Gainer, Esq., for a full day in mid-February. The plaintiff's counsel asked Dr. Lee questions, in order to conduct their own investigation of the ALFSG issue. They recorded his answers and drafted the declaration for Dr. Lee to review. As shown by evidence provided by the defendants, multiple drafts were exchanged between Dr. Lee/his counsel and plaintiff's counsel. After a final review, Dr. Lee signed and adopted the declaration.

Dr. Lee made extensive changes, including a request to remove statements that the FDA was provided with the case report forms. See Doc. No. 214, Ex. D. Plaintiff's counsel, admittedly, neglected to make this edit before submitting the final draft to Dr. Lee for his signature. From what has been provided, this appears to have been an oversight. I see no prejudice to the defendants, especially now that the record has been corrected. Striking the declaration from the record seems a harsh and unwarranted sanction. The other arguments the defendants offered were either irrelevant to whether Dr. Lee's declaration warrants exclusion or are unpersuasive.

After the plaintiff filed the amended declaration by Dr. Lee, the defendants also made an epistolary request for the court to order the plaintiff to amend her other filings, claiming that these included "misstatements" based on the errors in Dr. Lee's declaration. I denied this request as well. This was unnecessary. I have read the plaintiff's filings, all other filings on this issue, and considered only Dr. Lee's amended declaration in deciding the ALFSG motions. I have no problem recognizing the appropriate facts to consider in light of the corrected declaration. I see no prejudice to the defendants in denying this request.

I also note that even if Dr. Lee's declaration had been striken, Drs. Larson and Robuck provided similar information about the ALFSG data. My decision on these motions would not have changed.

- A declaration by Patricia Robuck, Ph.D., M.P.H., a former ALFSG Project Officer for the NIH/NIDDKD who supervised the ALFSG studies.[91]

After reviewing the plaintiff's evidence, I find she has met her burden; the Larson article is reliable, relevant, and survives any Daubert challenge. It may be relied on and discussed by plaintiff's experts in expressing their opinions on causation.[92]

A. Facial Review of Larson "Low-dose" Case Data Provides No Evidence that the Larson Methodology is Unreliable[93]

A judge only need to find that there are "good grounds" for a methodology to be reliable. The methodology need not be perfect.[94] A judge can find that the "scientist's methodology has some flaws such that if they had been corrected, the scientist would

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[91] Dr. Robuck is not a paid consultant, expert, or party to this case. See P. Robuck Dep., Apr. 18, 2016 at 10, 13 (Doc. No. 216, Ex. 4).

The plaintiff also offers supplemental expert reports by Timothy Davern, M.D. (co-Author of the Larson Article), Neil Kaplowitz, M.D., and Laura Plunkett, Ph.D., DABT, along with an expert report of Randall L. Tackett, Ph.D. I have not considered these expert opinions in making my decision. The defendants have moved to exclude Drs. Davern, Kaplowitz, and Plunkett; those Daubert motions are still pending. The plaintiff had not previously disclosed using Dr. Tackett in this litigation.

[92] The admissibility of the opinions of each individual causation expert on this point is a separate question. That question will be answered by the pending Daubert motions challenging Dr. Blume's, Dr. Kaplowitz's, Dr. Nelson's, Dr. Davern's, and Dr. Plunkett's opinions.

[93] The defendants also seem to take issue with plaintiff's experts' opinion that acetaminophen has a "narrow margin of safety." As the plaintiff points out, this conclusion is one that is generally accepted in the scientific community studying this issue. See In re: Tylenol (Acetaminophen) Marketing, Sales Practices and Prods. Liab. Litig. (Terry v. McNeil-PPC, Inc., et al.), Order, November 15, 2015 (Design Defect)(Doc No. 286). The defense experts in this case also admit this. See S. Flamm Dep., Apr. 8, 2016 at 80-81, 291-92 (Doc. No. 206, Ex. E.). However, I will further discuss this issue when I rule on the Daubert motions to exclude the individual plaintiff's experts, if appropriate.

[94] The defendants cite In re Denture Cream Prods. Liab. Litig., 2015 WL 392021 (S.D. Fla. Jan. 28, 2015), for the proposition that opinions based on flawed studies should be excluded. While it's true that In re Denture Cream excluded an expert's opinion based on a specific study, the court's reasons for making this exclusion were not simply because the study itself was scientifically unsound. Instead, the court explained that the study was not on point to answer the key question in the case—whether the zinc-containing denture creams caused copper deficiency myeloneuropathy (CDM). Id. at *2, *20-26. The study was intended "to review cases of severe copper deficiency and 'assess[ ] their hematological and neurological symptoms and signs, to further characterize the condition and identify signs that might prompt early treatment," not to identify or explore the link between dental creams and CDM. Id. at *23-25. This case is distinguishable.

have reached a different result" yet still find that there are "good grounds" for the scientific evidence presented. See In re Paoli R.R. Yard PCB Litigation, 35 F.3d 717, 744 (3d Cir. 1994).

Evidence from the plaintiff supports both the meticulousness of the ALFSG's procedures and the reliability of the data. [95] The initial data for the study was collected at the various ALFSG sites by site investigators.[96] The site investigators recorded their data on standard case report forms.[97] This data, along with the forms, was then sent to USTW, the central site for the ALFSG.[98] The data and forms were then reviewed at UTSW and entered into a spreadsheet.[99]

When a patient met the criteria for being enrolled in the study, the site investigators recorded a dosing history, the type of acetaminophen taken (when possible),

[95] Dr. Flamm recognizes that the Larson article is not the only published article reporting acetaminophen-induced liver damage at low doses. The other well-cited article is by plaintiff's expert Dr. Neil Kaplowitz. See S. Flamm Dep., Apr. 8, 2016 at 291-92 (Doc. No. 206, Ex. E)("Q. But you do believe toxicity can occur at 5, 6 or 7, but not acute liver failure until 7.5. Q. True? A. I think toxicity -- I think liver injury can occur at lower doses of acetaminophen as demonstrated by Kaplowitz and Watkins, yes. And then I don't think, as I stated I believe, that liver failure can occur at doses lower than 7.5.") and at 81 ("Q. You're not going to dispute that hepatotoxicity can occur with people ingesting 7 grams per day, are you? A. I am not. Q. Because that's the scientific truth? A. There are good papers to support that contention, including one by Kaplowitz and Watkins."). The plaintiff also points to other evidence of low-dose cases from the FDA's own adverse event report database. The fact that other sources have observed acetaminophen-induced liver injury at recommended doses further undercuts the defendants' argument.

[96] See A. Larson Dep., Apr. 22, 2016 at 66-67, 94-99 (Doc. No. 216, Ex. 6).

[97] See A. Larson Dep., Apr. 22, 2016 at 66 (Doc. No. 216, Ex. 6).

[98] See P. Robuck Dep., Apr. 18, 2016 at 34 (Doc. No. 216, Ex. 4); A. Larson Dep., Apr. 22, 2016 at 66-67 (Doc. No. 216, Ex. 6); Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶¶ 28-31 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 28 (Doc. No. 220)(filed under seal).

[99] See A. Larson Dep., Apr. 22, 2016 at 66-67 (Doc. No. 216, Ex. 6).

duration of use, and medical history.[100] Whenever possible, the patient was interviewed about this information.[101] This is how doctors typically collect information about patient dosing.[102] When the patient wasn't available (i.e., unconscious), the patient's medical records and/or family members were consulted for information.[103] This is a standard procedure used in all ALFSG studies, not just the Larson article.[104] The limitations of recording dosing history were disclosed in the paper itself.[105]

Investigators at the individual sites would determine the diagnosis; investigators at UTSW (the central site) would then review the case report forms to confirm the diagnosis.[106] After identifying their initial group of eligible patients, the authors excluded patients whose case files lacked appropriate data or failed to identify likely competing

[100] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶¶ 26, 28, 29, 37(b)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶¶ 35, 48(b)(Doc. No. 220)(filed under seal); A. Larson Dep., Apr. 22, 2016 at 69 (Doc. No. 216, Ex. 6). See also Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1365 (Doc. No. 193, Ex. A).

[101] See A. Larson Dep., Apr. 22, 2016 at 69 (Doc. No. 216, Ex. 6)("The primary person to ask about dosing and what they took is the patient.") and at 71 (same).

[102] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 37(b)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 48(b)(Doc. No. 220)(filed under seal); A. Larson Dep., Apr. 22, 2016 at 74 (Doc. No. 216, Ex. 6).

[103] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶¶ 28, 29 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 69-70 (Doc. No. 216, Ex. 6). See also Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1365 (Doc. No. 193, Ex. A).

[104] See https://www.niddkrepository.org/studies/aalf/ (stating "Eligibility criteria for patients with ALF include: Altered mentation of any degree (encephalopathy); Evidence of moderately severe coagulopathy (INR $\geq$ 1.5); Presumed acute illness onset of less than 26 weeks; Informed consent from patient's next of kin).

[105] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 27 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶¶ 35, 48(b)(Doc. No. 220)(filed under seal).

[106] See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1365 (Doc. No. 193, Ex. A); A. Larson Dep., Apr. 22, 2016 at 66-69 (Doc. No. 216, Ex. 6).

causes.[107] Those involved in the study carefully weighed the evidence collected.[108] In cases where Drs. Lee or Larson questioned the accuracy of the reported case information, they contacted the site investigator to confirm the information.[109] When they got clarifying information, this was added directly to the case report form.[110] In addition, the

[107] The initial cohort included 302 enrollees; 27 were excluded bringing the total enrollment to 275. See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 14 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 61, 126-27 (Doc. No. 216, Ex. 6); William Lee, M.D. Dec., May 10, 2016 at ¶ 36 (Doc. No. 220)(filed under seal). This was disclosed in the article itself. See Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1365 (Doc. No. 193, Ex. A).

[108] See P. Robuck Dep., Apr. 18, 2016 at 24, 93 (Doc. No. 216, Ex. 4)(stating that the low-dose cases were discussed at oversight meetings about the study). Dr. Larson herself did the intake for six of the 19 cases. See A. Larson Dep., Apr. 22, 2016 at 94-95, 107 (Doc. No. 216, Ex. 6).

[109] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶¶ 30 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal) and at 37(b)("Where there were questions [about dose], we attempted to query the original site to get as much accurate information as possible. When we got clarifying information we usually noted it directly on the CRF form (notations which McNeil's experts sometimes misinterpret as 'conflicting' information)"); A. Larson Dep., Apr. 22, 2016 at 60-61, 69 (Doc. No. 216, Ex. 6); William Lee, M.D. Dec., May 10, 2016 at ¶¶ 28(d), 48(b)(Doc. No. 220)(filed under seal)("Where we had questions or concerns, we attempted to query the site to get as much accurate information as possible…When we got clarifying information we noted it directly on the CRF form usually with the writer's initials to indicate an edit based on additional information provided by the site (notations which McNeil's experts sometimes misinterpret as 'conflicting' information)."); Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 47(B)(Pl. Ex. 2).

In fact, one of the 19 cases was queried by the ALFSG about whether the dosing history and diagnosis were correct. The site confirmed that their data was accurate. Ironically, this case was being supervised by Dr. Flamm, who signed off on the accuracy of the dose. See Anne Larson, M.D. Dec., Mar. 17, 2016 at 13-14 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at 10 (Doc. No. 220)(filed under seal). See also A. Larson Dep., Apr. 22, 2016 at 86-90 (Doc. No. 216, Ex. 6)(discussing Flamm's case).

[110] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 37(b)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 118 (Doc. No. 216, Ex. 6); William Lee, M.D. Dec., May 10, 2016 at ¶¶ 28(i), 48(b)(Doc. No. 220)(filed under seal).

The defense experts assumed notations added after the initial form was completed by a different investigator somehow rendered the data faulty. This defies logic. In the realm of science, a method which provides for revision and correction is seen as more reliable than one which collects data without further review. See also P. Robuck Dep., Apr. 18, 2016 at 41-42 (Doc. No. 216, Ex. 4)("I've been doing clinical trials for a very, very long time. And sometimes during the course of a study more information comes to light. And when that happens, then there are changes to be made.").

The defendants also argue that "inconsistencies" in the Medications List render the methodology faulty. Drs. Larson and Lee explained that initially investigators only included medications other than acetaminophen in the medications list because there was a separate area to report acetaminophen specifically; in later years, acetaminophen may have been noted in both places. See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 38 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at 17, 19 (Doc. No. 220)(filed under seal). This

FDA and NIH oversaw the collection of the ALFSG data and subjected the ALFSG data to additional peer-review.[111] Dr. Lee also visited the sites periodically to do quality assurance reviews of the case report forms.[112]

The Larson article's methodology follows appropriate and reliable procedures under the dictates of the federal rules and Daubert.[113]

"inconsistency" is not so "large" as to warrant exclusion of the article. See In re Paoli, 35 F.3d at 746 ("The judge should only exclude the evidence if the flaw is large enough that the expert lacks 'good grounds' for his or her conclusions.").

[111] See Patricia Robuck, Ph.D., M.P.H., Dec., Mar. 16, 2016 at ¶¶ 3-4, 7-10, 12, 14-15 (Pl. Response to Def. Motion to Exclude, Ex. 3, under seal); P. Robuck Dep., Apr. 18, 2016 at 21, 31-33, 42, 57-60, 91, 103-04, 116-21, 123-28 (Doc. No. 216, Ex. 4). See also William Lee, M.D. Dec., May 10, 2016 at ¶ 25 (Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 24 (Doc. 216, Ex. 3)("Q. How often does NIH review the grant for Acute Liver Failure Study Groups? A. We have, basically in the last three cycles, gotten five years of funding, so we have to go back every five years for renewal. Q. And when you go back, is it a process that you have to submit a lot of substantive information to get refunded? A. There's several steps. You have to go through an external advisory committee to the NIH that reviews what you've performed to date even before you're allowed to submit a grant. And then once you submit the grant, it undergoes a second review, again, by independent investigators with some expertise in the area, but no obvious conflicts of interest with us. And then they give a recommendation to the NIH. Q. Okay. So it's a -- would it be fair to say that it's basically a peer reviewed process of your entire program? A. Yes."); A. Larson Dep., Apr. 22, 2016 at 18-19 (Doc. No. 216, Ex. 6).

[112] See William Lee, M.D. Dec., May 10, 2016 at ¶ 28(k)(Doc. No. 220)(filed under seal). See also Larson, et. al., Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study, Hepatology 2005; 42(6):1364-1372, 1365 (Doc. No. 193, Ex. A)(noting annual on-site audits by UTSW/central site).

[113] The defendants imply that the Larson article is no more than a series of case reports. See Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1336-41 (11th Cir. 2010)(affirming district court's exclusion of plaintiff's general causation expert in case involving pain pump because expert's sources included review of anecdotal case reports and no epidemiological studies); DeGidio v. Centocor Ortho Biotech, Inc., 3 F. Supp.3d 674, 677-88 (N.D. Ohio 2014)(excluding experts' causation opinion because were based on case reports that were dissimilar to issue in case and because the experts' methodology in extrapolating from those reports was flawed and unreliable). This implication underscores the level of scrutiny and care taken by the ALFSG medical professionals in gathering the Larson data and the oversight processes implemented by the FDA and NIH.

While it is true that the ALFSG relied on patients' own self-reporting of dosage when the patients' mental state may have been altered, follow up studies by the ALFSG has shown that dose data collected from patients is often accurate despite the patients' altered mental state. See W. Lee Dep., Apr. 14, 2016 at 99 (Doc. No. 216, Ex. 3)("Q. Okay. Do you think that that's a valid criticism of your paper, that you relied on medical histories?...A. We disclose that we relied on dosing information from the patients and their families. Q. Do doctors in their clinical practice and in particular in your research with the Acute Liver Failure Study Group have to rely oftentimes on what patients tell you? …A. We always take a history. Medical students are taught to take a history. And we do seek accuracy....Q. …Is it true, Doctor, that all patient information provided is inaccurate? A. No. Q. Have you actually studied whether or not the patients providing medical history in low doses have provided accurate histories? A. We've attempted to go back and question patients after they've recovered as to whether the dose that was reported in the chart initially, whatever means was used to obtain it, corroborated with what their recall was, let's say, four or five days later when they were about to leave the hospital. Q. And what did you find? A. There was a pretty remarkable

B. Adduct Testing Confirms Causation on Most Cases[114]

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correlation between the two numbers. Q. And what does that tell you? A. It seems to affirm that the original history was reasonably accurate."); A. Larson Dep., Apr. 22, 2016 at 117 (Doc. No. 216, Ex. 6)("Q. Okay. Have you had occasion to go back, afterwards, and re-interview the patients? A. Yes. Q. Would you tell us what you found when you go back and re-interview patients? A. If the patient survives, and you talk to them, they frequently will tell you almost exactly the same thing, about their dosing or-- rarely a patient will admit to a suicide attempt and change their story, but for the most part they're remarkably similar.").

The ALFSG investigators also used differential diagnosis to rule out other possible causes of the patients' conditions. Compare DeGidio v. Centocor Ortho Biotech, Inc., 3 F. Supp.3d 674, 684-85 (N.D. Ohio 2014)(explaining what makes case reports unreliable). In this way, these case reports do not simply record adverse events of patients but, instead, entailed more exacting controls on the accuracy of the data. Compare Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 537-44 (W.D. Pa. 2003)(finding case reports to be unreliable and "unscientific" bases for causation opinion because are unpublished, not peer-reviewed, did not consider alternative causes, patients' medical history, etc.); McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1250 (11th Cir. 2005)(explaining that anecdotal information "without any medical controls or scientific assessment" is unreliable basis for expert opinion); Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1211 (10th Cir. 2002)(finding that exclusion of opinions based on case reports with little information about medical history appropriate but that case reports with more detailed information may be reliable source of expert opinion).

[114] The defense experts claim that the adduct results correlate to dose. See S. Flamm Dep., Apr. 8, 2016 at 127-39 (Doc. No. 206, Ex. E); J. Brent Dep., Mar 30, 2016 at 94-129 (Doc. No. 206, Ex. D). The defense experts cite Dr. Lee for this proposition. However, Dr. Lee testified that adduct values do not correlate to dosing. See W. Lee Dep., Apr. 14, 2016 at 119-21 (Doc. No. 216, Ex. 3)("Q. Now, there's been some suggestions by McNeil's litigation experts that the higher the adduct value, the higher the dose the patient must have taken. Do you understand that to be what they have testified to? A. Yes, I understand that. Q. Okay. Is that an accurate interpretation of the science that you have been in the process of developing? A. No. Q. Okay. Have acetaminophen adducts been shown to determine the amount of acetaminophens taken and when you take it? A. Not to my knowledge. Q. There's also been some testimony on Friday from Dr. Flamm, which I can show you if you wish, that suggested that anything over 1.1 is by definition an overdose to the effect of 25 to 50 grams. Is that true? A. Not to my knowledge. Q. Have you ever said anything like that? A. No. Q. Okay. If he testified that you said that to the FDA, would that be an accurate . . . A. No. Q. If anyone were to stand up in court and say, 'The presence of acetaminophen adducts over 1.1 proves that a patient took more than 4 grams,' would that be true? A. No. Q. If anyone were to stand up in court and say, 'Dr. Lee himself told the FDA that acetaminophen adduct greater than 1.0 means that a patient took 25 to 50 grams of acetaminophen,' would that be true? A. No. Q. Doctor, what do the results on Table 1 in your declaration actually show in terms of the reliability of the low-dose data in the Larson paper? A. It confirms that each of the people with a level above 1.1 had taken an amount to cause liver toxicity. Again, the James definition is that the level greater than 1.1 is associated with enzyme levels higher than 1,000. It doesn't say anything about dose administered."). See also A. Larson Dep., Apr. 22, 2016 at 81 (Doc. No. 216, Ex. 6)("Q Do you say that 'Because measurement of serum NAPQI-protein adducts reliably identify at least 17 acetaminophen dose'? A No, they don't identify dose. Q Okay. Would that be inaccurate if I substitute 'dose' for "toxicity" in your sentence? A Yes.").

The defendants only offer one article to support this correlation, N. Khandelwal, et al., "Unrecognized Acetaminophen Toxicity as a Cause of 'Indeterminate' Acute Liver Failure," Hepatology, 2011 February; 53(2): 567-576. Drs. Lee and Larson were named authors on the article. The article indicates that an adduct concentration of greater than or equal to 1.0 nmol/mL serum shows a definite acetaminophen overdose. However, it is not clear from the article what the authors mean by "overdose"—does this mean above 4 grams (the recommended daily dose at the time it was published) or do they simply mean "unsafe or non-therapeutic" dose? See W. Lee Dep., Apr. 14, 2016 at 237-38 (Doc. No. 216, Ex. 3)("A. You read it correctly, but I guess the -- if you drill down on what do you mean by 'overdose,' it might be that somebody who gets toxicity with ALT elevation over 1,000, for them an overdose could be 3 grams. I mean, 'overdose' is a gen- -- generic word. I don't think you can apply it strictly to the 4-gram-per-day dose. Q. Do you stand by the statement that's published in Khandelwal 2011, that 'an adduct concentration over 1.0 of serum indicated a definite acetaminophen overdose'?...A. I just said I'm -- I'm not sure that

The plaintiff has also offered objective scientific evidence from Dr. Lee and Dr. Larson confirming that the patient's liver damage in 16 of the 19 cases was, in fact, caused by acetaminophen.[115] After the Larson article was published, scientists and medical professionals developed the acetaminophen-adduct assay. This test can show whether ALF was caused by acetaminophen or whether another cause was the source of the hepatologic injury.

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we used the word properly or -- or that the definition of overdose is as clear as you would like it to be."); A. Larson Dep., Apr. 22, 2016 at 82 (Doc. No. 216, Ex. 6)("Q…When you use the word 'overdose,' what do you mean? A. I mean they develop toxicity, so for them the dose they took created toxicity. Q. Okay. So could somebody have an overdose for them at four grams or three grams? A. Potentially.").

They simply make a correlation between a certain serum level and a "clinically defined APAP overdose" without actually stating what defines a "clinically defined APAP overdose." This article did not discuss dose. Its purpose was not to correlate adduct levels to dose. Instead, its conclusion was that adduct levels could predict unrecognized acetaminophen-induced ALF—an important development since 18% of clinicians in the study did not diagnose it as the cause without the test. See N. Khandelwal, et al., "Unrecognized Acetaminophen Toxicity as a Cause of 'Indeterminate' Acute Liver Failure," Hepatology, 2011 February; 53(2): 567-576. I do not find this article to offer support for the defendants' theory that adduct levels correlate to dose. See also James, et al., "Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure," Drug Metabolism and Disposition, Vol. 37, No. 8, 1779-1784, 1781 (2009)(Doc. No. 206, Ex. S.)("No correlation was observed between reported APAP dose and peak APAP adduct (r= 0.03).") and at 1783 (explaining how the data in the article only applies to single overdose cases not unintentional chronic dosing acetaminophen-induced ALF). The Khandelwal article also explained that the timing of the last dose and whether an individual received the antidote may affect what adduct level is reported (making a dosing correlation more difficult to assess). See N. Khandelwal, et al., "Unrecognized Acetaminophen Toxicity as a Cause of 'Indeterminate' Acute Liver Failure," Hepatology, 2011 February; 53(2): 567-576.

In Dr. Lee's deposition, the defendants reference another article by Dr. James, claiming it noted a correlation between adducts and dosage. See W. Lee Dep., Apr. 14, 2016 at 246 (Doc. No. 216, Ex. 3). However, the defendants have not provided a copy of this article. Dr. Lee was unable to comment on the article because he was unaware of it until his deposition. Even if this article does stand for that proposition, a single article does not establish that this conclusion would necessarily be correct.

Lastly, the defendants' theory is discredited by evidence put forth by the plaintiff that shows the adducts testing in the low-dose hospital case were high, yet all other information indicates that the dose would have been at or below recommended doses. See W. Lee Dep., Apr. 14, 2016 at 363-65 (Doc. No. 216, Ex. 3)(discussing hospital case and adduct/dose correlation); A. Larson Dep., Apr. 22, 2016 at 93-94 (Doc. No. 216, Ex. 6)(same). The defendants' arguments on this point are unpersuasive.

[115] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 37(e)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 47-48 (Doc. No. 216, Ex. 6); William Lee, M.D. Dec., May 10, 2016 at ¶¶ 47, 48(d)(Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 115-18, 122 (Doc. No. 216, Ex. 3).

The adduct assay tests for serum acetaminophen-protein adducts—chemical compounds formed when NAPQI (the acetaminophen toxic byproduct that typically gets neutralized by glutathione, an antioxidant found in the liver) binds to cysteine groups on liver proteins, when glutathione is not present.[116] If there are a high level of adducts in the blood, then acetaminophen is the cause of the liver damage.[117] It has been tested and proven to show causation of ALF by acetaminophen.[118] This test is helpful in diagnosing unintentional acetaminophen-induced ALF cases because patients don't exhibit the same symptoms as intentional OD/suicide attempts (i.e., no psychosis issues presented to hint at suicide).[119]

Drs. Lee and Larson went back to their original samples in the Larson data and tested 18 cases for adducts.[120] One case could not be tested.[121] Of those 18, 16 tested

[116] See A. Larson Dep., Apr. 22, 2016 at 166 (Doc. No. 216, Ex. 6)("A Adducts merely measure the byproduct of toxicity. Q And the byproduct of acetaminophen toxicity is NAPQI? A Yes."); R. Dart, B. Rumack, "Central Nervous System Agents," Acetaminophen, Sec. 8, Chap. 126, 723-38, 726 in Medical Toxicology (3rd Ed.)(2004)(Doc. No. 206, Ex. O); N. Khandelwal, et al., "Unrecognized Acetaminophen Toxicity as a Cause of 'Indeterminate' Acute Liver Failure," Hepatology, 2011 February; 53(2): 567-576, 568.

[117] See W. Lee Dep., Apr. 14, 2016 at 95-96 (Doc. No. 216, Ex. 3)("Q…Could you describe what the acetaminophen adducts test is? A. The adduct assay was developed at the University of Arkansas at Little Rock, based on the finding and biopsies of both mice exposed to acetaminophen as well as people, that the product of the cell damage could actually be both identified in the tissue and in serum samples, in blood samples. And that's identified with a very specific method called 'high pressure liquid chromatography with electrochemical detection,' abbreviated, HPLC with ED. And that method is very specific and sensitive to detect not the parent compound, not acetaminophen itself, but the byproduct of the toxicity, not just the metabolic product but the product that's associated with liver damage."); A. Larson Dep., Apr. 22, 2016 at 44-46 (Doc. No. 216, Ex. 6).

[118] See S. Flamm Dep., Apr. 8, 2016 at 89 (Doc. No. 206, Ex. E.)("Q. And the assays are now considered to be the gold standard for acetaminophen causation as it relates to acute liver failure. True?... A. Yes."); William Lee, M.D. Dec., May 10, 2016 at ¶ 48(d)(Doc. No. 220)(filed under seal).

[119] See, e.g., N. Khandelwal, et al., "Unrecognized Acetaminophen Toxicity as a Cause of 'Indeterminate' Acute Liver Failure," Hepatology, 2011 February; 53(2): 567-576.

[120] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 37(e)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 48-49 (Doc. No. 216, Ex. 6).

within the toxic range for adducts (meaning, acetaminophen was the cause of the liver damage).[122] One of the 18 was not reported as being in the toxic range; however, Drs. Larson and Lee noted that the sample on this case was taken almost a week after the patient's last dose. This delay may have skewed this result lower than it actually was because the adducts had likely been processed out of the patient's system during that week since the patient's last dose.[123] The other case that did not test positive for adducts Drs. Lee and Larson admit was likely not an appropriate case to include in the study. In hindsight, they believe the liver injury was caused by Macrobid not acetaminophen.[124]

C. Review by Drs. Lee and Larson

As part of their declarations, Drs. Larson and Lee again reviewed the 19 cases to determine whether their conclusions remained the same.[125] Drs. Larson and Lee are not paid experts in this case and remain third-party fact witnesses.[126]

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[121] See also Anne Larson, M.D. Dec., Mar. 17, 2016 at 10-11 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 21 (Doc. No. 220)(filed under seal).

[122] See Anne Larson, M.D. Dec., Mar. 17, 2016 at 6 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 47 (Doc. No. 220)(filed under seal).

[123] See Anne Larson, M.D. Dec., Mar. 17, 2016 at 12 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 47, 30 (Doc. No. 220)(filed under seal). I note that Drs. Lee and Larson still consider this case to be a "low-dose" acetaminophen-induced ALF case based on the information available.

[124] See Anne Larson, M.D. Dec., Mar. 17, 2016 at 14 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 110-111 (Doc. No. 216, Ex. 6); William Lee, M.D. Dec., May 10, 2016 at 38 (Doc. No. 220)(filed under seal).

[125] See William Lee, M.D. Dec., May 10, 2016 at ¶¶ 6, 16-47 (Doc. No. 220)(filed under seal); Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 9, 6-16 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal).

[126] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 14 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 23 (Doc. No. 216, Ex. 6); William Lee, M.D. Dec., May 10, 2016 at ¶ 7 (Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 44-47 (Doc. No. 216, Ex. 3). Dr. Lee refused to be a paid consultant for the plaintiff. See William Lee, M.D. Dec., May 10, 2016 at ¶ 7 (Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 44-47 (Doc. No. 216, Ex. 3)..

Drs. Lee and Larson admit that 1 of the 19 cases should not be included in the "low-dose" category of the study but still involved acetaminophen-induced ALF.[127] This case noted that the patient had taken 6 grams of acetaminophen over 2 days (i.e., 3 grams a day, making it less than 4 grams a day) when, in fact, it appears the individual took 6 grams of acetaminophen for 2 days. Though the case would not be a "low-dose," Drs. Lee and Larson point out that the dose reported is still relatively low—essentially the person took two more doses (i.e., equivalent to 4 more Extra Strength Tylenol tablets) a day than was recommended. This case still supports the article's conclusion that acetaminophen has a "narrow therapeutic margin of safety."

Drs. Lee and Larson also admitted that one of the 19 cases was not caused by acetaminophen-induced ALF, as shown by the adduct testing.[128] In that case, the liver injury was likely caused by Macrobid or nitrofurantoin.[129] Drs. Lee and Larson still believe the case which could not be tested for adducts was caused by acetaminophen

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[127] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 11 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 108-09 (Doc. No. 216, Ex. 6); William Lee, M.D. Dec., May 10, 2016 at ¶¶ 6, 47 and at 47 (Doc. No. 220)(filed under seal); W. Lee Dep., Apr. 14, 2016 at 123-24 (Doc. No. 216, Ex. 3).

[128] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 37(e)(Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 6 (Doc. No. 220)(filed under seal).

The defendants argue that the admitted exclusion of 2 cases from the 19 cases by Drs. Lee and Larson renders their findings statistically unsound. The sample size of 19 cases is too small to draw any statistically significant conclusions. See W. Lee Dep., Apr. 14, 2016 at 280-81 (Doc. No. 216, Ex. 3)(discussing how two cases out of 275 do not render all findings of the study unreliable).

Furthermore, Dr. Lee stated in his declaration that 240 of the 275 cases from the Larson article were later tested for adducts. In this later study, 93.5% of those cases tested positive for adducts. See William Lee, M.D. Dec., May 10, 2016 at ¶ 48(d)(Doc. No. 220)(filed under seal). Though this number does not include all 275 cases from the Larson article, it offers a better indication of whether the Larson article's conclusions regarding causation were accurate. From this information, it appears that the Larson article's findings remain scientifically sound.

[129] See Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 10 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); William Lee, M.D. Dec., May 10, 2016 at ¶ 47 (Doc. No. 220)(filed under seal).

based on the other data in the file.[130] Overall, Drs. Lee and Larson conclude that 17 of the 19 cases remain properly categorized as "low-dose" acetaminophen-induced ALF cases and acetaminophen would still, in their opinion, be the cause of liver injury for 18 cases of those cases. [131]

Despite the alterations in Drs. Lee and Larson's findings in the Larson article, I find the article to be admissible. I did not find the alleged deficiencies in the handling of the 19 low-dose cases to be so egregious to render the article unreliable. See In re Denture Cream Prods. Liab. Litig., 2015 WL 392021, at *11 (S.D. Fla. Jan. 28, 2015)(finding that "the myriad, serious methodological flaws in the Fixodent Blockade Study" warranted exclusion; "taken together, the Court finds Fixodent Blockade Study is not 'good science,' and is not admissible." (citing Daubert, 509 U.S. at 593)). It is typical for studies to have some flaws. No study is perfect nor every piece of data entirely accurate.[132] Any flaws in the Larson article analysis should be brought out on cross-examination of its authors. "Vigorous cross-examination, presentation of contrary

[130] See William Lee, M.D. Dec., May 10, 2016 at 25 (Doc. No. 220)(filed under seal).

[131] See William Lee, M.D. Dec., May 10, 2016 at ¶ 6 (Doc. No. 220)(filed under seal); Anne Larson, M.D. Dec., Mar. 17, 2016 at ¶ 13 (Pl. Response to Def. Motion to Exclude, Ex. 2, under seal); A. Larson Dep., Apr. 22, 2016 at 33 (Doc. No. 216, Ex. 6).

Dr. Lee also testified that a case in which the reported dose was 1200 mg would be considered a "weak case." However, he did not exclude it as a low-dose case, after-the-fact. See W. Lee Dep., Apr. 14, 2016 at 269-280 (Doc. No. 216, Ex. 3). This point goes more to weight than admissibility.

[132] See P. Robuck Dep., Apr. 18, 2016 at 122 (Doc. No. 216, Ex. 4)("I have never been involved with 4 any study in all the years that I've been involved with this that had all the i's dotted and all the t's crossed. There will always be outliers. There will always be data that cannot be collected. There will always be exemptions or inclusions. There will always be flaws. What we try very, very hard to do is, A, describe all of these exceptions, if you will, in publications to be truthful in how we present the data with these. And that we also strive that we keep the errors, if you will, down to a dull roar. A study that has 80% accuracy and that has all of the data is phenomenal.") and at 135 ("Because there are always flaws in every single solitary study, even at the highest level. There is no such thing as a perfect dataset. I wish there was. There's no such thing as an errorless case report form. I can tell you this. If I found out that there was something wrong with this data, I would stake my reputation that Dr. Lee did not know about it.").

evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 586 (1993). Any concerns about the article's analysis or conclusions go to weight, not admissibility.

For the reasons stated above, I will deny the defendants' motion to exclude the use of the Larson article under Daubert.

V. CONCLUSION

For the foregoing reasons, I will **GRANT** the plaintiff's motion to strike defendants' supplemental opinions on the validity of the Larson article and will **DENY** the defendants' motion to exclude the use of the Larson article under Daubert.

An appropriate Order follows.